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CRISTIANO DE QUEIROZ MENDONÇA

ALTERAÇÕES OFTALMOLÓGICAS EM PACIENTES PEDIÁTRICOS COM LEUCEMIA LINFOBLÁSTICA AGUDA

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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Sergipe como requisito para obtenção de título de Doutor em Ciências da Saúde.

Orientadora: Profa Dra Rosana Cipolotti

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RESUMO

Introdução: Leucemia Linfoblástica Aguda (LLA) é o câncer mais comumente encontrado entre os jovens, responsável por 26% dos casos de câncer infantil, com taxa de sobrevida de doença de 90% em cinco anos. As manifestações oculares (MO) decorrentes das LLAs podem estar relacionadas à infiltração direta do olho e da órbita pelas células neoplásicas, serem secundárias às anormalidades vasculares tumor-induzidas ou a medicações usadas no tratamento como quimioterápicos e glicocorticoides (GC). Por ser doença oncológica com alto potencial de cura, em indivíduos jovens com elevada expectativa de vida, a identificação de eventuais complicações oculares de longo prazo decorrentes do tratamento e a correlação com fatores preditivos de recaída da doença poderá subsidiar o delineamento de um protocolo oftalmológico para esses casos. **Objetivo:** Caracterizar as MO em pacientes pediátricos com LLA e avaliar se estão associados a fatores de risco preditivos para recaída, com os protocolos (1999 ou 2009), gênero e infiltração liquórica. **Métodos:** Realizado estudo de coorte prospectivo em crianças e adolescentes com LLA, de janeiro de 2013 a dezembro de 2017, seguido de estudo de revisão sistemática, associando pacientes pediátricos em tratamento para LLA e hipertensão ocular (HO), devido a HO ser a MO mais prevalente. No estudo da coorte os pacientes foram submetidos a avaliações oftalmológicas antes do início do tratamento (D0), no oitavo dia (D8), no 28º dia (D28) e aos seis meses (D6 meses). A HO foi definida quando o resultado da aferição da pressão ocular foi >21 mmHg. Medidas de acuidade visual (AV) <20/40 foram consideradas como baixa visão (BAV). **Resultados:** Os resultados da coorte envolveram 55 pacientes e destes, 33% apresentaram MO. As principais foram HO (20%) , hemorragia retiniana (7,3%) e BAV (7,3%). Forte associação foi encontrada entre pacientes com MO e alto risco de recaída ($p = 0,035$, Cramer V = 0,31) e os que usaram o protocolo de 1999 ($p = 0,022$, Cramer V = 0,32). O risco de MO em pacientes do protocolo de 1999 foi de 1,8 (IC = 1,154-2,804) e o risco de MO em pacientes de alto risco foi de 1,6 (IC= 1,111-2,442). Os resultados da revisão sistemática limitaram-se a quatro publicações sendo dois de relatos de casos individuais, um relato de cinco pacientes e outro descritivo prospectivo com doze pacientes, com resultados variando de total controle da pressão ocular e conservação da AV, até cegueira irreversível. **Conclusão:** Pacientes pediátricos com LLA têm alta incidência de MO devido ao tratamento e à própria doença, podendo ser assintomáticos ou evoluírem com complicações que podem chegar a BAV. Aqueles submetidos ao protocolo de 1999 e com alto risco de recaída são os mais propensos a apresentar MO e essas variáveis estão fortemente associadas. A HO é a MO mais prevalente. Poucos estudos foram encontrados correlacionando crianças com LLA e HO, com resultados variando de HO silenciosa, sem alterações visuais, até cegueira irreversível. Portanto, é proposto um protocolo que contemple exame oftalmológico sistemático com a medida da PIO imediatamente após o diagnóstico de LLA (D0) e, posteriormente, em D8, D28 e D6meses.

Descritores: Leucemia linfoblástica aguda. Glaucoma. Esteroides. Quimioterapia.

ABSTRACT

Introduction: Acute Lymphoblastic Leukemia (ALL) is a cancer commonly found among young people and responsible for 26% of childhood cancer cases. Today, up to 90% of such patients have an average survival rate of five-year free of the illness. Ocular manifestations (OM) arising from ALLs might be secondary to tumor-induced vascular anomalies or related to direct infiltration of the neoplastic cells into the eye and orbit, or to medications used in treatment such as chemotherapy and glucocorticoids (GC). Since this is an oncological disease with a high potential for cure, in young individuals with a high life expectancy, the identification of possible long-term ocular complications resulting from the treatment and correlation with predictive factors of relapse of the disease may support the design of an ophthalmological protocol for these patients cases. yet existent in scientific literature. **Objective:** To characterize OM in pediatric patients under treatment for ALL and to evaluate if they are associated with predictive risk factors for relapse, with protocols (1999 or 2009), gender and cerebrospinal fluid (CSF) infiltration **Methods:** A prospective cohort study was conducted in children and adolescents with ALL from January 2013 to December 2017, followed by a systematic review associating pediatric patients under treatment for ALL and ocular hypertension (OH), because OH is the most prevalent OM. The patients underwent ophthalmologic evaluations before starting treatment (D0), on the eighth day (D8), at the 28th day (D28), and at six months (D6 months). Ocular hypertension (OH) was considered in results above 21 mmHg. Measures of visual acuity (VA) <20/40 were considered visual loss (VL). **Results:** The results of the cohort involved 55 patients and 18 (32.7%) presented OM, been OH (20.0%), retinal hemorrhage (7.3%) and VL (7.3%) the most frequent finds. A strong association was found between patients with OM and those with a high risk of relapse (p=0.035, Cramer V=0.31) and who used the 1999 protocol (p=0.022, Cramer V=0.32). The risk of OM in patients from the 1999 protocol was 1,799 (CI=1,154-2,804), while in those at high risk of relapse it was 1,647 (CI=1,111-2,442). The results of the systematic review were limited to a total of four publications, two of individual case reports, one report of five patients and another prospective descriptive with twelve patients, with results varying from total ocular pressure control and VA preservation, to irreversible blindness. **Conclusion:** Patients with ALL have a high incidence of OM due to the treatment and the disease itself, and it may even be asymptomatic and evolve with VL. Patients submitted to the 1999 protocol and at high risk of relapse are more likely to present OM and these variables are strongly associated. OH is the most prevalent OM. Few studies have been found correlating children with ALL and OH. Due to the possibility of disparate results from silent OH without visual changes to irreversible blindness. Therefore, a protocol is proposed that contemplates systematic ophthalmological examination with the measurement of IOP immediately after diagnosis of ALL (D0) and subsequently at D8, D28 and D6months.

Descriptors: acute lymphoblastic leukemia. Glaucoma. Steroids. Chemotherapy.

LISTA DE ABREVIATURAS E SIGLAS

ALL	*Acute Lymphoblastic Leukemia*
AR	Alto risco de recaída da doença
BR	Baixo risco de recaída da doença
CSF	*Cerebrospinal fluid*
D0	Dia anterior ao início do tratamento
D14	Décimo quarto dia de tratamento
D28	Vigésimo oitavo dia de tratamento
D8	Oitavo dia de tratamento
D6meses	Sexto mês de tratamento
GC	Glicocorticóides e *glucocorticoids*
GR	Gen receptor de glicocorticoide (GR-NR3C1)
HO	Hipertensão Ocular
IOP	*Intraocular pressure*
LLA	Leucemia Linfoblástica Aguda
LnH	Linfoma não-Hodgkin
MO	Manifestações oculares
MMP_2	Matriz de metaloproteinase-2
NHL	*Non-Hodgkin Lymphoma*
OCT	Tomógrafo de Coerência Óptica
OD	Olho direito
OE	Olho esquerdo
OH	*Ocular hypertension*
OM	*Ocular manifestations*
PIO	Pressão intraocular
POAG	Glaucoma primário de ângulo aberto

TM	Malha trabecular do ângulo da câmara anterior ocular
TPA	Activador do plasminogênio tecidual
VA	*Visual acuity*
VL	*Visual loss*

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1 INTRODUÇÃO

A leucemia linfoblástica aguda (LLA) é, na faixa pediátrica, o câncer mais comum e responde por aproximadamente 26% dos casos de câncer infantil (WARD et al., 2014). A LLA corresponde a 80% dos casos diagnosticados em pacientes de zero a 14 anos e aproximadamente 56% dos casos em adolescentes acima dos 14 anos. Nos últimos 30 anos, os avanços científicos se traduziram em melhorias nas propostas terapêuticas que culminaram numa redução da mortalidade por LLA em mais de 30% (WARD et al., 2014). Atualmente tais pacientes possuem, em média, sobrevida livre de doença de até 90% em cinco anos (MARCOUX et al., 2016; WARD et al., 2014).

Apesar do sucesso do tratamento quimioterápico para LLA, vários estudos apontam para alterações tardias em diversos órgãos e sistemas, incluindo os domínios emocional e cognitivo (ALLEMANI et al., 2015; BERBIS et al., 2014; HONG et al., 2014; MERTENS et al., 2014; WHELAN et al., 2010). Lesões oculares e orbitais são a terceira manifestação extramedular mais comum da LLA, depois das lesões meníngeas e testiculares, variando entre 43 a 90% dos casos de LLA (CHARIF et al., 2002, SHARMA et al., 2004; TALCOTT; GARG, R.; GARG, S., 2016).

As MO tanto podem estar relacionadas à infiltração direta do olho e da órbita pelas células neoplásicas, quanto serem secundárias à anormalidades vasculares tumor-induzida ou a complicações pelo uso de medicamentos quimioterápicos, incluindo altas doses de glicicorticoides (GC) (MENDONCA et al., 2014; RAZEGHINEJAD; KATZ, 2012).

Por se tratar de uma doença oncológica com grande potencial de cura e que compromete indivíduos com elevada expectativa de vida, é importante caracterizar as MO de pacientes pediátricos em tratamento para LLA, bem como avaliar se tais manifestações possuem correlação com preditores de risco de recidiva definidos na literatura e outros fatores como protocolo de tratamento quimioterápico, idade, gênero, óbito, imunofenotipagem e infiltração do liquor por células neoplásicas. Identificar e tratar precocemente tais alterações oculares pode prevenir dano permanente à visão, além de diagnosticar precocemente uma possível infiltração ou recidiva incipiente da doença.

2 REVISÃO DA LITERATURA

A LLA constitui 26% de todas as neoplasias em indivíduos de zero a 15 anos, constituindo 80% das leucemias infantis. Seu pico de incidência ocorre entre dois e cinco anos de idade, com média de idade de 6,5 anos, sendo discretamente mais frequente no sexo masculino, em indivíduos de cor branca e de países desenvolvidos (WARD et al., 2014; YEOH et al., 2013; YOUNG et al., 1986). História familiar está presente em 5% dos casos (YASMEEN; ASHRAF, 2009; YOUNG et al., 1986).

As taxas de LLA variaram cerca de 10 vezes entre 54 populações estudadas, sendo mais elevadas em hispânicos brancos dos EUA, seguido pelo Equador, e sendo mais baixas na população negra dos EUA, Tunísia e Uganda. Essa variação quanto à distribuição geográfica pode ser atribuída a fatores de risco ambientais, genética e/ou diferenças nos critérios de diagnóstico e no tratamento (LINET et al., 2015). Estudos epidemiológicos de câncer na América do Sul não são comumente relatados. A mediana da taxa de incidência ajustada de leucemia no Brasil e na Argentina foi de 47 por milhão (DE CAMARGO et al., 2010; MORENO et al., 2013). No Brasil, em Recife-PE, estudo estimou em cerca de 48,5 casos por milhão de crianças e adolescentes (LINS et al., 2016).

Em virtude dos avanços no tratamento, a taxa de mortalidade da LLA declinou mais de 30% nos últimos 30 anos (WARD et al., 2014). Por se tratar de uma neoplasia maligna das células precursoras de linfócitos, caracterizada pela aberração na proliferação e diferenciação dos precursores linfoides, a LLA acarreta falência do sistema imunológico e decréscimo na hematopoese normal, resultando em anemia, trombocitopenia e neutropenia. É comum ao exame a presença de anemia (86%), linfadenopatia (75%), hepatomegalia (67%) e esplenomegalia (58%). Inicialmente pode haver leucocitose elevada (>50.000/mm^3), observada em 34% dos pacientes, hemoglobina <7g/dl em 54%, plaquetopenia <20.000/mm^3 em 33% e comprometimento de sistema nervoso central em 5% (YASMEEN; ASHRAF, 2009).

Os pacientes são classificados no momento do diagnóstico em dois grupos, de acordo com o risco de recidiva. Os pacientes com alto risco de recaída (AR) são aqueles que preencheram um dos seguintes critérios: idade igual ou superior a nove anos, contagem de leucócitos maior que ou igual a 50.000 células/mm^3 no momento do diagnóstico e

imunofenotipagem compatível com LLA de células T. O grupo de baixo risco (BR) engloba os pacientes que não preenchem nenhum dos critérios acima (CERDÀ-IBÁÑEZ et al., 2018).

Existem diferenças notáveis entre os países de baixa e média renda em comparação com os países desenvolvidos em relação aos índices de mortalidade durante a indução, mortalidade aos seis meses após o diagnóstico (início da fase de manutenção), infiltração no líquido cefalorraquidiano e proporção de pacientes alto risco de recaída. Essas diferenças estão mais diretamente relacionadas ao acesso à infraestrutura adequada para o tratamento de complicações do que aos aspectos biológicos da doença (HOWARD et al., 2008).

Hoje, nos país desenvolvidos, uma criança com diagnóstico de LLA tem uma expectativa de sobrevida média em cinco anos de até 90%, com 95% de probabilidade de viver mais 10 anos passados os cinco iniciais (MARCOUX et al., 2016; WARD et al., 2014). A Sociedade Americana de Câncer mostra que em 2016, 6590 novos casos foram diagnosticados, com 1400 mortes secundárias à LLA (TERWILLIGER; ABDUL-HAY, 2017).

O tratamento consiste em quatro a seis semanas de quimioterapia de indução inicialmente administrada no hospital, seguida por vários meses de quimioterapia de consolidação (geralmente até os seis meses do início do tratamento) e dois a três anos de quimioterapia de manutenção (MARGOLIN et al., 2010). Os mais recentes protocolos de tratamento da LLA utilizados no Brasil foram propostos em 1999 e atualizados em 2009 (ALL-99 e ALL-09) pelo “Grupo Brasileiro de Tratamento da Leucemia Linfoblástica Aguda na Infância” da Sociedade Brasileira de Oncologia Pediátrica. Ao final dos primeiros 28 dias de tratamento (D28) o protocolo ALL-99 previa uma dosagem total de 1120 mg/m^2 de Prednisona para o grupo BR e 1680 mg/m^2 de Prednisona para o grupo AR. O protocolo ALL-09 previa 420 mg/m^2 de prednisona e 126 mg/m^2 de dexametasona para o grupo BR e 1260 mg/m^2 de prednisona para o grupo AR (BRANDALISE et al., 2010; WATANABE, 2007).

Apesar do sucesso do tratamento quimioterápico para LLA, vários estudos apontam para alterações tardias em diversos órgãos e sistemas, incluindo os domínios emocional e cognitivo, deficiência de crescimento, risco aumentado para o aparecimento de novo câncer como Leucemia Mieloide Aguda ou Linfoma, tumor de sistema nervoso central e de pescoço (BERBIS et al., 2014; HONG et al., 2014; MERTENS et al., 2014; WARD et al., 2014; WHELAN et al., 2010). Lesões oculares e orbitais são a terceira manifestação extramedular mais comum da leucemia aguda, depois das lesões meníngeas e testiculares (CHARIF et al., 2002; GORDON et al., 2001).

2.1 Manifestações Oculares

De maneira geral, a fisiopatologia do acometimento ocular na LLA deve-se a três mecanismos principais: I) infiltração direta do olho e órbita pelas células neoplásicas; II) anormalidades vasculares afetando a retina ou III) acometimento neuro-oftalmológico (REDDY; MENON, 1998). No primeiro caso pode-se ter invasão de coroide, hifema, hipópio, heterocromia da íris, glaucoma secundário, proptose, episclerite (ÇAÇA et al., 2005; YALCINBAYIR et al., 2017); no segundo, hemorragias retinianas, manchas de Roth, exsudatos algodonosos, oclusões vasculares, descolamento de retina, microaneurismas, dilatação e tortuosidade venosa (ÇAÇA et al., 2005; CHAUDHURI; ROY, S.; ROY, P., 2013; YALCINBAYIR et al., 2017); no terceiro, a infiltração do nervo óptico pode acarretar paralisia de nervos cranianos e papiledema (SHARMA et al., 2004). Entre as anormalidades retinianas, uma revisão observou 24% de hemorragias retinianas, 11% de manchas de Roth e 16% de exsudatos (TALCOTT; GARG, R.; GARG, S., 2016). Mais frequente parece ser a infiltração da coroide, estimada em 50 a 82% dos casos (GORDON et al., 2001).

Envolvimento ocular pode ser classificado em duas principais categorias: primária ou infiltração leucêmica direta, e secundária ou envolvimento indireto (SHARMA et al., 2004). A infiltração leucêmica direta pode ser observada em três diferentes padrões: (a) infiltração uveal, infiltração orbital, e sinais neuro-oftalmológicos de infiltração nervosa (CHAUDHURI; ROY, S.; ROY, P., 2013; LIN et al., 2005), (b) paralisia de nervos cranianos e (c) papiledema (NGUYEN; HAIDER; ACKERMAN, 2013). As alterações secundárias são manifestações retinianas, hemorragia vítrea, infecções, e oclusões vasculares devido as anormalidades hematológicas da leucemia como anemia, trombocitopenia, hiperviscosidade e imunodepressão (SHUYUAN; MING; YUNXIA, 2018).

2.1.1 Manifestações primárias

A córnea é uma estrutura avascular e, portanto, não é comumente envolvida na leucemia, especialmente na forma de invasão direta de células leucêmicas. Pode haver envolvimento da córnea além do envolvimento do limbo (ALLEN; STRAATSMA, 1961). Alterações corneanas são também vistas quando o seu epitélio se transforma devido ao

tratamento quimioterápico. Essas mudanças incluem adelgaçamento irregular, maturação defeituosa e queratinização (JABS et al., 1983). Apesar de o envolvimento da conjuntiva não ser uma apresentação comum da leucemia, ocorre mais comumente em pacientes em leucemias linfoides (DUKE-ELDER, 1965).

Infiltração da esclera é geralmente um achado de autópsia e ocorre em leucemias agudas. Essas células são achadas mais frequentemente na episclera em um padrão perivascular (ALLEN; STRAATSMA, 1961).

Clinicamente, infiltração evidente da íris por células leucêmicas não é comum. Isso ocorre com o envolvimento da coroide e do corpo ciliar e é clinicamente caracterizado por mudança na cor da íris e um pseudohipópio, de coloração cinza/amarelada (PERRY; MALLEN, 1979). Leucemias foram identificadas como a doença de base em 5% dos casos de uveítes na pediatria (SOYLU; OZDEMIR; ANLI, 1997).

A coroide demonstra infiltração leucêmica mais consistentemente no exame histopatológico, embora, clinicamente, a retina seja a parte mais envolvida na leucemia. O envolvimento da coroide por células leucêmicas tende a ser perivascular e desigual ou difuso (ALLEN; STRAATSMA, 1961).

AO envolvimento retiniano é estimado em até 69% de todos os pacientes com leucemia mostram alteração de fundo de olho em algum ponto durante o curso da doença (ALEMAYEHU et al., 1996). As manifestações precoces, por conta dos distúrbios hematológicos, são dilatação e tortuosidade venosa (BALLANTYNE; MICHAELSON, 1970). As hemorragias e infiltrações são vistas em todos os níveis da retina, especialmente nas camadas interiores com destruição focal. Os infiltrados e agregados de células leucêmicas são geralmente vistos em torno das áreas hemorrágicas. A membrana limitante interna frequentemente atua como uma eficiente barreira contra a infiltração de células leucêmicas. (KUWUBARA; AIELLO, 1964). Contudo, células leucêmicas ocasionalmente invadem o vítreo possivelmente emergindo da cabeça do nervo óptico (REESE; GUY, 1976).

Como consequência do aumento na sobrevida, o envolvimento do sistema nervoso e do nervo óptico se tornou mais frequente, particularmente na leucemia aguda. Pode aparecer, mesmo quando a medula óssea está em remissão, já que a barreira hematoencefálica restringe a livre passagem de certos agentes quimioterápicos (RIDGWAY; JAFFE; WALTON, 1976; SHAW et al., 1960). Infiltração do sistema nervoso central ocorre tanto em adulto, menos comum, quanto em crianças (DAWSON; ROSENTHAL; MOLONEY, 1973) e mais comumente em LLA comparado às Leucemias Mieloides Agudas (HYMAN et al., 1965).

Infiltração orbital na leucemia se apresenta como exoftalmia, edema palpebral e dor (CAVDAR et al., 1971; COLOMBINI et al., 1995). Todos os tipos de leucemia podem atingir a órbita, porém o envolvimento orbital é mais comum nas leucemias agudas comparadas as crônicas e ocorrem mais comumente em leucemias linfoides quando comparas as mielóides (JAKOBIEC; JONES, 1979).

Outras alterações oculares menos comuns da leucemia incluem necrose do segmento anterior, dacriocistite e infiltração da pele (CULLIS; HINES; BULLOCK, 1952).

2.1.2 Manifestações Secundárias

Pacientes com leucemia, durante o período de neutropenia, são mais suscetíveis a desenvolver infecções incomuns e que ameacem a vida. Esses pacientes são suscetíveis a uma ampla variedade de infecções virais, fúngicas, bacterianas e de protozoários (COGAN, 1977). Uma das infecções mais comuns nos imunocomprometidos é por citomegalovírus (CMV) (SHIBATA et al., 1997), que invade a retina, causando necrose, hemorragia, e combina descolamento exsudativo e regmatogênico da retina (MEREDITH; AABERG; REESER, 1979). Outros vírus (herpes simples, varicela zoster e caxumba) também podem causar retinite necrotizante em pacientes imunocomprometidos (COGAN, 1977). Herpes zoster também pode causar úlcera corneal periférica, ceratite e esclerite (WALTON; REED, 1999).

Os fungos são a causa mais comum de infecções oculares nas leucemias. Infecção por Candida causa uveíte e retinite com infiltratos algodonosos no vítreo. Outra infecção fúngica comum em pacientes com leucemia é por Aspergillus (COGAN, 1977).

Infecção bacterina por Pseudomonas é comum em pacientes imunossuprimidos. Essa infecção pode iniciar como blefaroconjutivite e se estender causando celulite orbitária (GIAGOUNIDIS et al., 1997).

Sintomas oculares podem desenvolver-se após transplante da medula óssea, tanto pela doença enxerto *versus* hospedeiro como pela radioterapia de corpo inteiro, que integra protocolos de condicionamento que antecedem o transplante de medula óssea. Melhorias recentes no manejo geral desses pacientes têm resultado no reconhecimento mais frequente dos problemas oculares. MO da síndrome enxerto *versus* hospedeiro incluem ceratoconjuntivite sicca, lagoftalmo cicatricial, conjuntivite por pseudomonas ou estéril, defeitos epiteliais, úlcera corneana, uveíte e ectrópio da pálpebra (CLAES; KESTELYN, 2000: KASMANN; RUPRECHT, 1993).

Nos últimos anos foram introduzidas muitas novas drogas anticancerosas, tanto na prática clínica quanto como parte de protocolos de pesquisa. Para muitos destes, a ampla gama de efeitos colaterais ainda não é conhecida. Bussulfan, por exemplo, foi identificado como causa de catarata subcapsular posterior (RAVINDRANATHAN; PAUL; KURIAKOSE, 1972). Vincristina e vinblastina são tóxicos ao sistema nervoso e afetam principalmente os nervos periféricos, podendo acometer os motores ocular e do trigêmeo. Vincristina também foi apontada como causa de atrofia óptica (SHURIN; REKATE; ANNABLE, 1982).

Os GC, por sua vez, usados em dose imunossupressora durante a fase de indução e manutenção, aumentam significativamente o risco de o paciente desenvolver catarata subcapsular posterior, seu principal efeito colateral. Segundo estudo, esse risco é cinco vezes maior quando comparados os pacientes curados com seus irmãos sadios (ESSIG et al., 2014). Outro efeito importante é a Hipertensão Ocular (HO) e glaucoma iatrogênico pelo uso de GC, o glaucoma cortisônico (KERSEY; BROADWAY, 2005; MENDONCA et al., 2014; RAZEGHINEJAD; KATZ, 2012).

2.1.3 Glaucoma Cortisônico e Hipertensão Ocular

A descoberta dos GC foi um grande avanço no tratamento de várias doenças. À semelhança de outros agentes terapêuticos, têm seus próprios efeitos colaterais, incluindo HO e glaucoma iatrogênico (RAZEGHINEJAD; KATZ, 2012).

O glaucoma é a principal causa de cegueira irreversível, mas previnível, do mundo. Tem como principal causa o aumento da Pressão Intra Ocular (PIO) (POMORSKA et al., 2012), que é mais frequentemente aferida pela técnica de tonometria de aplanação após instilação de anestesia local (proparacaina a 0,5%) e corante de fluoresceína (GOLDMAN, 1957).

A incidência de glaucoma na infância é de 2,29/100 000 pessoas com idade inferior a 20 anos. O glaucoma infantil é uma patologia pediátrica incomum, associada a significante perda visual. Consiste de um grupo heterogêneo de doenças que geram neuropatia óptica e perda de campo visual, e que pode ser classificado em primário, secundário e adquirido (APONTE; DIEHL; MOHNEY, 2010) .

Glaucoma primário é geralmente dividido em congênito (cujo início se dá desde o nascimento até o final do período de recém-nascido) e primário juvenil de ângulo aberto (cujo início se dá mais frequentemente dos quatro anos até o período de adulto jovem). O glaucoma

primário congênito é o principal tipo observado na infância (APONTE; DIEHL; MOHNEY, 2010). Ainda no grupo dos glaucomas congênitos, os secundários associam-se a alterações sindrômicas ou a outras condições presentes ao nascimento, como aniridia, sídrome de Axenfeld-Rieger, retinopatia da prematuridade, síndrome de Rubinstein-Taybi, síndrome de Sturge-Weber, persistência do vítreo hiperplástico primário e rubéola congênita (APONTE; DIEHL; MOHNEY, 2010). Glaucoma adquirido é resultado de outros processos não presentes ao nascimento como inflamação, drogas (como GC), trauma e cirurgia (APONTE; DIEHL; MOHNEY, 2010).

HO induzida por GC foi primeiramente descrita em 1950 com a observação de glaucoma em associação com a administração de GC sistêmico (MCLEAN, 1950). As rotas mais comuns de indução HO são a administração tópica, intra-ocular ou periocular. Pode também ocorrer depois de uso sistêmico, aplicação na pele , intranasal, ou por inalação (URBAN; DREYER, 1993). Estudo prévio mostrou possibilidade de HO em valores elevados, em criança com Síndrome Nefrótica, usuária de GC (BRITO et al., 2012). Geralmente ocorre com algumas semanas de uso de GC em paciente suceptíveis, mas é geralmente reversível com a descontinuação do tratamento. Entretanto, se o tratamento for prolongado, pode resultar em neuropatia óptica (NG et al, 2008; SPAETH; BARROS; FUDEMBERG, 2009; QASHTON, 2011). As alterações glaucomatológicas comprometem não somente o nervo óptico como também interferem nos mecanismos que causam elevação da PIO, como aumentando a resistência à drenagem do humor aquoso pela malha trabecular (TM) (CLARK; WORDINGER, 2009; DANIAS et al., 2011). Além disso, o aumento da PIO pode ser pela própria infiltração da leucemia na malha trabecular (ROWAN; SLOAM, 1976).

Assim, o uso de GC podem acarretar HO e gerar uma patologia semelhante ao Glaucoma Crônico de Ângulo Aberto (POAG) (SCHWARTZ et al., 2002). Estudos em pacientes tratados com potentes GC tópicos ou sistêmicos mostraram o desenvolvimento de HO em 30 a 40% dos casos, pela diminuição da drenagem do humor aquoso associada a modificações morfológicas na TM (ARMALY; BECKER, 1965) devido ao maior acúmulo de proteínas como a fibronectina e miocilina além da degradação do ativador do plasminogênio tecidual (TPA), e/ou matriz de metaloproteinase-2 (MMP_2) responsáveis pela homeostasia do sistema de drenagem do humor aquoso na câmara anterior, TM e consequentemente aumento da PIO (STAMER et al., 2013). Em adição, foi observado que pacientes mais sensíveis ao uso de GC possuem susceptibilidade maior para desenvolver POAG. Esses pacientes apresentam nível elevado de cortisol sérico e metabolismo anormal de cortisol ocular (CLARK; WORDINGER, 1995).

A administração de GC pode aumentar a PIO em 90% dos pacientes com POAG. Avaliando-se as pessoas normotensas oculares na população geral, a probabilidade de aumento da PIO com uso de GC é de 30-40%, caracterizando os médios-responsivos. PIO acima de 31 mm Hg ou 15 mm Hg acima do valor de base ocorre entre 4-6% dos casos, para os altos-responsivos (ZHANG; CLARK; YORIO, 2005). Até 5% dos pacientes não respondem ao tratamento medicamentoso e necessitam cirurgia (RAZEGHINEJAD; KATZ, 2012) .

Embora o glaucoma seja também observado em síndrome de Cushing, desencadeada pela produção de excesso endógeno de GC, a probabilidade de elevação da PIO pela administração de GC por via sistêmica é menor do que por via tópica. Geralmente os grupos de pacientes que estão sendo tratados com GC sistêmicos em longo prazo apresentaram maiores médias e maiores picos de valores de PIO que a população normal (HOVLAND; ELLIS, 1967; LEE, 1958). Um estudo encontrou uma incidência de 10% de glaucoma em pacientes transplantados renais que receberam GC (ADHIKARY; SELLS; BASU, 1982). Há correlação positiva entre a PIO e dose de GC (aumento de 1,4 mmHg na PIO média para cada aumento de 10 mg na dose diária média de prednisona administrada) (TRIPATHI et al., 1992).

Vários relatos de casos clínicos mostram aumento da PIO após o uso de GC em crianças (BRITO et al., 2012; THAM et al., 2004; YAMASHITA et al., 2010). Com a suspensão do tratamento a pressão normalmente retorna a níveis normais. Por outro lado, o uso de GC sistêmicos pode gerar aumento assintomático da PIO, inclusive entre os pacientes pediátricos (NG et al., 2008).

Há sugestões da existência de diferenças genéticas entre os pacientes responsivos e não-responsivos. Alguns autores tentam explicar a susceptibilidade genética por mecanismo monozigótico autossômico: heterozigóticos para os médios-responsivos e os homozigóticos para os altos-responsivos (RAZEGHINEJAD; KATZ, 2011). Diversos mecanismos diferentes podem ser responsáveis para as sensibilidades GC entre os indivíduos, incluindo polimorfismos no gene GR (NR3C1), gene regulador do GC, e as diferenças na expressão do GR. A resposta ao GC é regulada pelos níveis relativos do receptor alfa (GRœ) e do regulador negativo (GRß). Linhagens de células da TM de pacientes glaucomatosos têm uma relação GRß-GRœ menor em comparação com as células TM normais, tornando-os mais sensíveis aos GCs (STAMER et al., 2013). Em situações de homeostase há produção normal de miocilina, fibronectina, glicosaminas e laminas, e degradação na TM do ativador do plasminogênio tecidual (TPA), e/ou matriz de metaloproteinase-2 (MMP_2) mediados pelo

GRß-GRœ. Quando há aumento da relação GRœ-GRß ocorre produção aumentada de miocilina e consequentemente menor drenagem de humor aquoso, predispondo ao aumento da PIO (PFEFFER et al., 2010; STAMER et al., 2013). A diminuição de GRß pode resultar no aumento da resposta ao GC e aumento da PIO (STAMER et al., 2013).

Estudos prévios têm mostrado que alterações morfológicas no nervo óptico e nas camadas de fibras nervosas do nervo óptico podem preceder alterações de campo de visão em pacientes com glaucoma (POMORSKA et al., 2012).

O conhecimento sobre as manifestações oculares da leucemia é importante para o diagnóstico e tratamento da doença, além de muitas vezes refletir o estágio da mesma no organismo. Estudos demonstram que a evidência de envolvimento ocular pode estar associada a pior prognóstico (CURTO et al., 1989; KINCAID; GREEN, 1983; REDDY; MENON, 1998).

Poucos estudos foram publicados especificamente relacionando MO em pacientes pediátricos tratados para LLA e nenhum deles foi elaborado de maneira sistemática e prospectiva. A identificação de eventuais complicações oculares de longo prazo decorrentes da própria doença e do tratamento, além de avaliar se as MO possuem correlação com preditores de risco de recidiva da doença e outros fatores (protocolo de tratamento quimioterápico, idade, gênero, óbito, imunofenotipagem e infiltração do CSF por células neoplásicas), poderá subsidiar o delineamento de um protocolo oftalmológico para esses casos.

3 OBJETIVOS

3.1 Objetivo Geral

- Avaliar as MO em pacientes pediátricos portadores de LLA.

3.2 Objetivos Específicos

- Identificar possíveis MO em pacientes pediáricos com LLA (artigo 1).
- Correlacionar se fatores prognósticos estabelecidos para recidiva de doença oncológica (tipo de protocolo de tratamento quimioterápico utilizado, sexo e infiltração do líquor por células neoplásicas) podem predizer risco de desenvolver MO (artigo 1).
- Descrever a produção científica nacional e internacional em forma de Revisão Sistemática da MO mais prevalente em pacientes pediátricos com LLA, a HO (artigo 2).

4 CASUÍSTICA E MÉTODOS

4.1 Casuística

4.1.1 Modelo de estudo, população, amostra e local do estudo

Foi desenvolvido um estudo de coorte prospectiva, realizado em pacientes pediátricos com diagnóstico de LLA, tratadas no período de 1 de julho de 2013 a 30 de dezembro de 2017 no Centro de Oncologia Dr. Oswaldo Leite (serviço público especializado em oncologia pediátrica do estado de Sergipe, região Nordeste do Brasil). Os pacientes elegíveis foram incluídos consecutivamente, após confirmação citopatológica e imunofenotípica do diagnóstico e após a anuência do responsável para o estudo de campo.

Realizou-se um estudo de Revisão Sistemática associando a MO mais prevalente em crianças com LLA, a HO.

4.1.2 Critérios de Inclusão para o Estudo

a) Diagnóstico de LLA confirmado laboratorialmente.

b) Idade até 19 anos incompletos.

c) Ausência de tratamento quimioterápico anterior.

d) Ausência de outra patologia por ocasião do diagnóstico.

e) Não utilização de GC sistêmico nos seis meses que antecederam o diagnóstico.

4.1.3 Critérios de Exclusão para o Estudo

a) Impossibilidade técnica.

b) Diagnóstico prévio compatível com glaucoma ou doença anterior relacionada a qualquer mudança na PIO.

4.2 Métodos

4.2.1 Estudo de Coorte (Artigo 1)

Pacientes elegíveis foram classificados ao diagnóstico em dois grupos conforme o risco de recaída da doença: pacientes com alto risco de recaída (AR): idade igual ou maior que nove anos, contagem de leucócitos maior ou igual a 50.000 células/mm³ no momento do diagnóstico e imunofenotipagem compatível com LLA de células T. O grupo de baixo risco de recaída (BR) compreendeu aqueles não inseridos em nenhum desses critérios.

Os protocolos de tratamento de LLA utilizados foram os propostos pelo "Grupo Brasileiro para tratamento da Leucemia Linfoide Aguda na Infância" em 1999 e atualizado em 2009 **(**ALL-99 e ALL-09). Foi utilizado como rotina de tratamento, o protocolo ALL-99 em todos pacientes admitidos até 31 de dezembro de 2014 e o ALL-09 após essa data.

Todos os pacientes foram submetidos a exame oftalmológico realizados por um único oftalmologista (C.Q.M.) conforme as técnicas e a periodicidade descritas a seguir. As avaliações foram efetuadas nos dias zero (D0), oitavo (D8), vigésimo oitavo (D28) dia do início do tratamento e com seis meses de tratamento (D6meses).

Os exames de D0 e D8 foram realizados no leito hospitalar devido à fragilidade da saúde desses pacientes quando do diagnóstico e consistiram em avaliação de segmento anterior ocular com lâmpada de fenda portátil, segmento posterior com oftalmoscopia direta

sem midríase e medida da PIO. Os exames de (D28) e (D6meses) foram realizados em um consultório oftalmológico especializado, sendo a análise de segmento anterior por biomicroscopia com lâmpada de fenda, o de segmento posterior através de oftalmoscopia indireta sob midríase induzida por tropicamida 0,01%, aferida a Acuidade Visual (AV) e a medida da PIO.

A PIO foi aferida por tonometria de aplanação com aparelho tipo Perkins, após anestesia local com colírio de proparacaína a 0,5% e corante de fluoresceína (GOLDMANN, 1957). Foram consideradas compatíveis com HO as medidas de PIO acima de 21 mmHg (CURTO et al., 1989).

A AV foi aferida com projetor automatizado de optotipos, com e sem midríase. Foi utilizado a tabela de Snellen e considerado baixa visual quando AV<20/40.

Os pacientes diagnosticados com qualquer patologia ocular receberam tratamento específico apropriado.

A análise dos dados foi feita utilizando-se o programa SPSS (*Statistical Package for Social Sciences*) 24.0. Variáveis categóricas foram descritas como frequência absolutas e relativas comparadas usando o teste exato de Fischer com o teste Cramer V para força e teste de ajuste multivariável de Benjamini-Hochberg para falsos positivos. As variáveis contínuas foram descritas em termos de média e desvio padrão. Foi utilizado também o teste Binomial para comparar proporções entre grupos não-paramétricos e o teste de Pearson para correlação de variáveis com distribuição normal. Foram considerados estatisticamente significativos os valores de $p<0,05$.

4.2.2 Estudo de Revisão Sistemática (Artigo 2)

Um protocolo da revisão sistemática foi registrado previamente no banco de dados PROSPERO (número de registro CRD42018087146).

Pesquisa bibliográfica foi realizada nas bases de dados: PubMed, Scopus, Web of Science, Science Direct, e Cochrane Library até 31 de janeiro de 2018. Uma pesquisa na literatura cinzenta foi realizada através do Google Scholar e OpenThesis. Os primeiros 100 resultados do Google Scholar foram registrados. A pesquisa também incluiu uma busca manual de referências cruzadas de artigos e resenhas originais.

A exposição foi definida como tratamento de LLA ou LNH com GC sistêmicos, independentemente do tipo de GC ou dosagem. O desfecho foi a HO ocorrida após o início do GC e definida como uma PIO superior a 21 mmHg em um ou ambos os olhos.

4.2.3 Considerações Éticas

O projeto foi aprovado pelo Comitê de Ética em Pesquisa envolvendo Seres Humanos da Universidade Federal de Sergipe (CEP-UFS), com número: 214.759. (APÊNDICE A)

5 RESULTADOS

5.1 Estudo de Coorte (Artigo 1)

Ocular Manifestations in Acute Lymphoblastic Leukemia: A Five-Year Cohort Study of Pediatric Patients

(Artigo aceito para publicação no Jornal: Leukemia Research, Manuscript Number: LR-D-18-00551R1).

ABSTRACT

Objective: To characterize ocular manifestations (OM) of pediatric patients treating for acute lymphoblastic leukemia (ALL) and to evaluate whether they are associated with well-described predictive risk factors for relapse, protocol (1999 or 2009), gender and cerebrospinal fluid infiltration. **Methods**: A prospective cohort study was conducted in children and adolescents with ALL from January 2013 to December 2017. The patients underwent ophthalmologic evaluations before starting treatment (D0), on the eighth day (D8), at the 28th day (D28), and at six months (D6 months). Ocular hypertension (OH) was

considered in results above 21 mmHg. Measures of visual acuity <20/40 were considered visual loss (VL) **Results**: Fifty-five patients were examined and 18 (32.7%) presented OM, been OH (61.1%), retinal hemorrhage (22.2%) and VL (22.2%) the most frequent finds. A strong association was found between patients with OM and those with a high risk of relapse (p=0.035, Cramer V=0.31) and who used the 1999 protocol (p=0.022, Cramer V=0.32). The risk of OM in patients from the 1999 protocol was 1,799 (CI=1,154-2,804), while in those at high risk of relapse it was 1,647 (CI=1,111-2,442). **Conclusions**: Patients with ALL have a high incidence of OM due to the treatment and the disease itself, and it may even be asymptomatic and evolve with VL. Of these, we can highlight OH as the most prevalent. Patients submitted to the 1999 protocol and at high risk of relapse are more likely to present OM and these variables are strongly associated.

Key words: acute lymphoblastic leukemia, glaucoma, steroids, chemotherapy

INTRODUCTION

Ocular manifestations in Acute Lymphoblastic Leukemia (ALL), varying from 43% to 90% depending on the study, are concerning because they are often silent [1,2]. Such manifestations often go unperceived since most patients are asymptomatic. Nevertheless, they can indicate a relapse or early worsening of the condition with a potential risk to the patient's sight.

Generally speaking, the physiopathology of ocular impairment in ALL is attributed to three main mechanisms: I) direct infiltration of the eye and orbit by the neoplastic cells; II) vascular abnormalities affecting the retina or III) neuro-ophthalmic impairment [3]. In the first case, there could be an invasion of the choroid, hyphemia, hypopyon, heterochromia of the iris, secondary glaucoma, proptosis and episcleritis [4,5]; in the second case, retinal hemorrhages, Roth spots, cotton wool exudation, vascular occlusions, retinal detachment, microaneurysms, as well as venal dilatation and tortuosity [4,5,6]; in the third case, infiltration of the optic nerve can lead to paralysis of cranial nerves and papilledema [2]. One revision observed retinal hemorrhages at 24%, Roth spots at 11% and exudates at 16% [1]. The most frequent appears to be an infiltration of the choroid, ranging from 50% to 82% of the cases [7].

Furthermore, the effects of chemotherapy on the patients' vision cannot be ignored. The use of high doses of glucocorticosteroids (GC) in the treatment entails a significantly

higher risk of developing other conditions, such as ocular hypertension (OH), cataracts, cortisone-induced glaucoma, dry eye, diplopia and blindness [8,9], which in some cases can persist even after ceasing treatment with the drug. Among the chemotherapeutic drugs, Vincristine is associated with alterations of ocular motricity, corneal hypoestesia, and optic atrophy [2]. Moreover, Methotrexate can induce alterations of motricity, such as internuclear ophthalmoplegia or optic neuropathy, with important repercussions for visual acuity [10]. Cytarabine, in turn, is associated with corneal toxicity [1].

This study characterized the ocular manifestations of pediatric patients during treatment for ALL and assessed whether such manifestations are associated with recurrence risk predictors defined in literature or with other factors, such as chemotherapeutic treatment protocols, gender, and infiltration of CSF. Early identification and treatment of such ocular alterations can prevent permanent visual loss, as well as precocious diagnosing of possible infiltration or incipient recurrence of the disease.

METHOD

A prospective cohort study was conducted with children and adolescents diagnosed with ALL, receiving treatment between January 1st, 2013 through to December 30th, 2017 at the only public service specialized in pediatric oncology in the state of Sergipe, Northeast region of Brazil. The project was approved by the Ethics Commission at the Federal University of Sergipe (CEP-UFS) which deals with research involving human beings, report number 214.759.

The patients were classified at diagnosis into two groups according to their risk of recurrence: patients with a high risk of relapse (HR) were those who met one of the following criteria: age equal to or greater than nine years, white cell count greater than or equal to 50.000 cells/mm^3 at the time of diagnosis, and immunophenotyping compatible with T-cell ALL. The low risk group (LR) encompassed those patients who did not meet any of the above criteria [11].

The ALL treatment protocols, used in this study, were proposed in 1999 and updated in 2009 (ALL-99 and ALL-09) by the "Brazilian Group for Treatment of Acute Lymphoblastic Leukemia during Infancy" of the Brazilian Society of Pediatric Oncology. At the end of the first 28 days of treatment (D28), the ALL-99 protocol called for a total dosage of 1120 mg/m^2 of Prednisone for the LR group and 1680 mg/m^2 of Prednisone for the HR

group [12]. The ALL-09 protocol calls for 420 mg/m^2 of Prednisone and 126 mg/m^2 of Dexamethasone for the LR group and 1260 mg/m^2 of Prednisone for the HR group.

The ALL-99 protocol was routinely used with all patients admitted until December 31th, 2014, whereas the ALL-09 was used for patients admitted afterwards.

In this study, patients were included whose diagnosis of ALL was confirmed by immunophenotyping of bone marrow or peripheral blood and who met all of the following criteria: at least one eye examination in the six-month follow-up period beginning at diagnosis, age below 19 years, absence of previous chemotherapeutic treatment, absence of prior ocular pathology, no use of systemic GC in the six months prior to the diagnosis and existence of technical conditions allowing for the performance of eye examinations.

The eye examination was carried out by a single ophthalmologist (C.Q.M.) and consisted of exams before the start of treatment (D0), on the eighth day after admission (D8), at the end of the remission induction phase, which corresponds to the 28th day of treatment (D28), and at the end of the six first months of treatment (D6months). The exams on D0 and D8 were performed on the hospital bed due to the fragile health of these patients at diagnosis and consisted of measurement of IOP, evaluations of the anterior chamber with a portable slit-lamp biomicroscope and of the posterior chamber with direct ophthalmoscopy, without mydriasis. The D28 and D6months examinations were performed at an ophthalmologist's office, analyzing the anterior chamber by slit-lamp biomicroscopy and the posterior chamber by indirect ophthalmoscopy after mydriasis induction with 0.01% Tropicamide, assessment of visual acuity (VA), and measurement of IOP.

In all exams, IOP was measured using a Perkins applanation tonometer, under local anesthesia with 0.5% Proparacaine eyedrops and Fluoresceine tracing dye. Intraocular pressure equal or superior to 21mmHg was considered compatible with OH [13].

Visual acuity was assessed with an optotype auto projector, with and without mydriasis. The Snellen chart was used and VA < 20/40 was considered VL.

Patients diagnosed with any ocular pathology received appropriate ophthalmological treatment.

Data analysis was performed using the SPSS (*Statistical Package for Social Sciences*) software, version 24.0. Categorical variables were described as absolute and relative frequencies and compared using Fischer's exact test with Cramer V-test for strength and the Benjamini-Hochberg False Discovery Rate test for multiple comparison correction. The

continuous variables were described in terms of average and standard deviation. The binomial test was also used to compare proportions between non-parametric groups and the Pearson's correlation test was used to analyze the relationship between normally-distributed variables. P-values < 0.05 were considered statistically significant.

RESULTS

Out of a total of 78 patients admitted to the service between 2013 and 2017, 67 met the inclusion criteria. However, 12 died before D8. Fifty-five patients had at least one eye examination between D8 and D6months. These patients were divided into two groups: those with normal examination results (n=37) and patients who presented some ocular manifestation (n=18). In turn, this last group was further divided into two groups depending on their visual acuity (Figure 1).

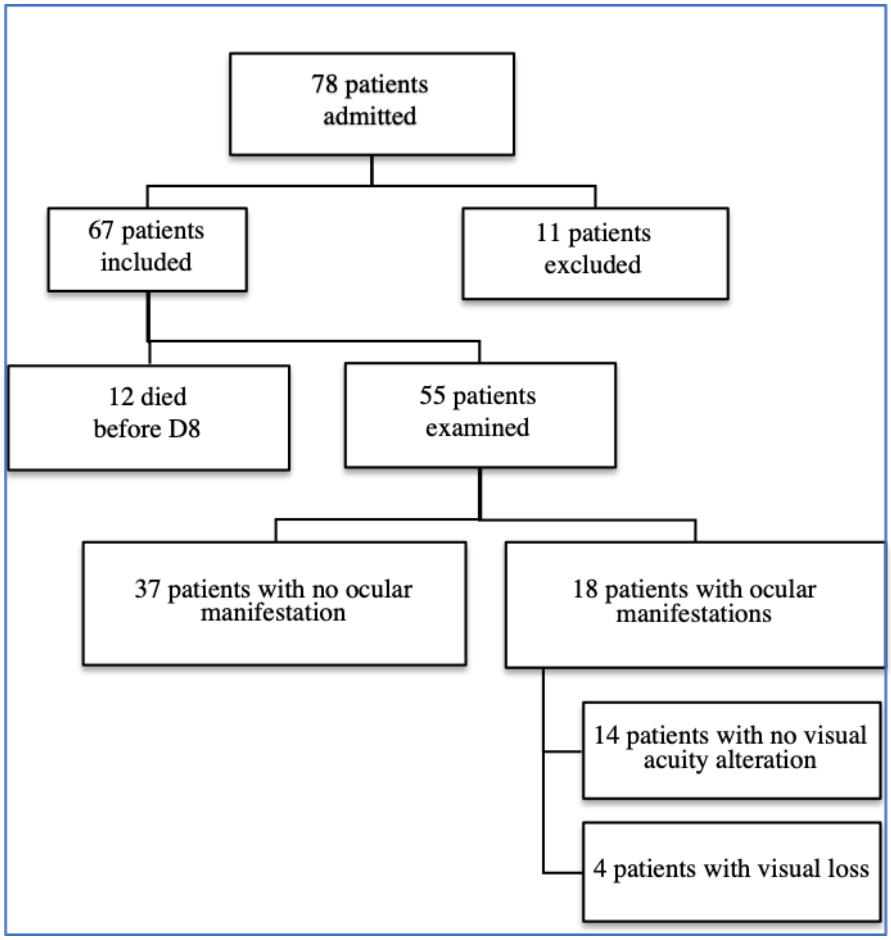

Figure 1: Flow chart showing the distribution of patients screened for possible ocular alterations in the cohort studied.

Sixty-seven patients with an average age of 9.10 years (SD = 5.436) were included, presented in Table 1 by protocol, gender, age range, risk, immunophenotyping, deaths, cerebrospinal fluid (CSF) infiltration and ocular manifestations.

Table 1. Profile of the patients included in the cohort

Variables	N (%)
Protocol	67
ALL-99	35 (52.2)
ALL-09	32 (47.8)
Gender	67
Feminine	30 (44.8)
Masculine	37 (55.2)
Age Range	67
< 9 Years	36 (53.7)
≥ 9 Years	31 (46.3)
Risk	65
Low	25 (38.5)
High	40 (61.5)
Immunophenotyping	67
B-Cell	62 (92.5)
T-Cell	5 (7.5)
Deaths	67
Yes	29 (43.3)
No	38 (56.7)
CSF Infiltration	22
Infiltrated	15 (68.2)
Negative	7 (31.8)
Ocular Manifestations	55
Present	18 (32.7)
Absent	37 (67.3)

The patients that presented ophthalmic alterations (N=18) were mainly from the ALL-99 protocol (77.8%), male (55.6%), older than 9 years-old (55.6%), high-risk (83.3%), B-cell Immunophenotype (83.3%), had not died during the 6-month follow-up (55.6%), and 50% of them presented infiltration of CSF in at least one examination. Patients with ophthalmic alterations, when compared to the group with normal examination results, predominantly used

the ALL-99 protocol (p=0.022) and belonged to the HR group (p=0.041). These results were confirmed by the Benjamini-Hochberg test with a false discovery rate of 20% and both associations are strong, according to the Cramer V-test (0.32 and 0.34, respectively). These results can be seen in Table 2.

Table 2. Comparison of patient groups with normal and altered ophthalmic examination for different variables.

Variables	Group with Ophthalmic Alterations N (%)	Group with Normal Exam Results N (%)	P Value*	Corrected P-value**
Protocol	18	37	0.022	0.029
ALL-99	14 (77.8)	16 (43.2)		
ALL-09	4 (22.2)	21 (56.8)		
Gender	18	37	1.000	0.200
Feminine	8 (44.4)	15 (40.5)		
Masculine	10 (55.6)	22 (59.5)		
Age Range	18	37	0.566	0.143
< 9 years	8 (44.4)	21 (56.8)		
≥ 9 years	10 (55.6)	16 (43.2)		
Risk	17	36	0.041	0.057
Low	3 (17.6)	18 (50.0)		
High	14 (82.4)	18 (50.0)		
Immunophenotyping	18	37	0.671	0.171
B-Cell	15 (83.3)	33 (89.2)		
T-Cell	3 (16.7)	4 (10.8)		
Deaths	18	37	0.213	0.086
Yes	8 (44.4)	9 (24.3)		
No	10 (55.6)	28 (75.7)		
CSF Infiltration	4	16	0.587	0.114
Altered	2 (50.0)	11 (68.8)		
Negative	2 (50.0)	5 (31.3)		

* Fisher exact-test

** Benjamini-Hochberg False Discovery Rate

Intra and/or extra-ocular alterations occurred in 32.7% of the patients examined, with a predominance of OH (61.1%), followed by retinal hemorrhage and VL (22.2%). Some

patients accumulated more than one alteration and the distribution of ophthalmic changes per patient is shown in Table 3.

Table 3. Distribution of eye manifestations per patient.

Patients	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
Alteration of retinal pigment epithelium																x		
Amaurosis															x			
Chorioretinal Atrophy															x			
Visual Loss		x													x	x	x	
Orbital Cellulitis			x															
Papilla Edema															x			
Retinal Hemorrhage				x	x										x	x		
Ocular Hypertension							x	x	x	x	x	x	x	x		x	x	x
Leukemic Infiltration																		x
Optic Nerve Pallor	x	x													x			
3rd Nerve Palsy															x			
Retinochoroiditis						x												
Uveitis from Herpes Zoster																	x	

When calculating the relative risk concerning the manifestation of ophthalmic changes using the cited variables, it was observed that the patients from the 1999 protocol have a risk 2.91 times higher for ocular manifestations than those from the 2009 protocol (CI 95% 1.099-

7.742) and low risk of relapse acting as a protective factor for presenting ocular manifestations (RR=0.327, CI 95% 0.107-0.999). These results are shown in Table 4.

Table 4. Relative risk of ocular manifestations.

	RR	CI 95%*
Deaths	1.788	0.859-3.722
Immunophenotype	0.729	0.281-1.891
CSF Infiltration	0.538	0.095-3.041
Protocol	2.917	1.099-7.742
Gender	1.113	0.521-2.379
Age Range	0.717	0.334-1.540
Risk of relapse	0.327	0.107-0.999

*95% confidence interval (CI)

The central tendency measurements with regard to IOP are shown using boxplots in Figure 2. It was observed that higher IOPs were found at D8, including some outliers with values of 24, 26 and 27 mmHg. The highest median was also observed at D8, approximately 17 mmHg. The lowest median, in turn, occurs at D6months, with a value of 14 mmHg. The greatest variation was observed at D28, whereas the smallest variations were observed to be similar at D0 and D6months.

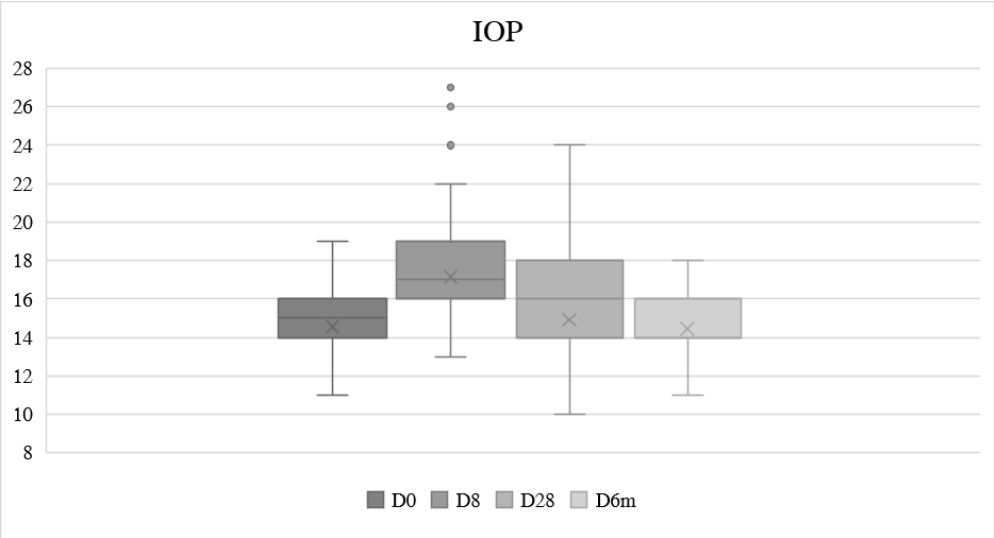

Figure 2: Boxplots showing the distribution of Intraocular Pressure in patients during the six-month follow-up period.

DISCUSSION

Childhood lymphoproliferative neoplasms most commonly attack B-cells and can affect the ocular appendix, including orbits, conjunctiva, eyelids and lacrimal glands [3]. Eye manifestations associated with the treatment of ALL are common, especially after the considerable increase in survival rate that followed the use of standardized multicentric protocols and better risk stratification, including the immunophenotyping of blasts. Furthermore, ocular impairment may be the first manifestation or sign of recurrence of the disease [13].

During the treatment, 32,7% of patients were confirmed as having ocular impairment, contrasting with previous studies that obtained 17%, 15%, 20% [3,14,16], but approaching others which found 29%, 39%, 38% [15, 17,18]. This data divergence is recurrent in the literature and reflects the application of different methods. Furthermore, in the present study, the highest proportion of ocular changes is due to the inclusion of the OH cases, which were actively traced in this cohort, even in the absence of symptoms, as was previously reported [9].

Risk of relapse acted as a protective factor, with a relative risk of 0.33, meaning that it is 67% less likely that one with low risk of relapse develop some ocular manifestation that one from the high-risk group, compatible with results in the literature [14]. This is also valid for those treated with the ALL-99 protocol, who had 2.91 times greater risk of presenting ocular manifestations than the ALL-09 patients, which could be explained by the lower total doses of GC in this group.

Direct ocular involvement occurred in one patient (2%) as leukemic infiltration of the optic nerve, an alteration observed in 7.3% of the cases in a previous study [15]. Among secondary ophthalmic alterations, the retina was the most affected tissue, with hemorrhage occurring in 7.3% of the cases, with similar proportions consistently described previously: 8% and 8.8% [3,16].

Other secondary alterations were the development of orbital cellulitis (2%) and uveitis due to Herpes zoster (2%). Patients with ALL can contract opportunistic germ infections and reactivate viral infections during the neutropenia phase, resulting in an elevated risk of death [19].

It was observed that during the remission induction phase, when high doses of GC are used, there was significant elevation of IOP in ten patients (20%), whose values were compatible with OH (IOP> 21mmHg). The result was greater than that presented in another study which reported 16.6% [9]. As in previous studies [3,9,13,14,15,19], no patient had developed isolated OH symptoms, making a diagnosis difficult when there is no systematic tracking of all patients.

Four patients suffered definitive visual impairment (7.3%) and none of those patients had developed isolated OH. These patients had other alterations secondary to the disease, such as retinal hemorrhage, optic nerve pallor, leukemic infiltration and uveitis, and suffered from reduced visual acuity.

There are remarkable differences observed between low and middle-income countries compared to that of developed countries in relation to indexes of mortality during induction, mortality at six months after diagnosis (the beginning of the maintenance phase), CSF infiltration and the proportion of patients with high risk of relapse [20]. These differences are more directly related to access to adequate infrastructure for treatment of complications than to the biological aspects of the disease. The data related to avoidable ocular complications, when promptly identified, can probably be generalized to apply to countries of all levels of income.

Thus, there exists the possibility of ocular involvement and silent OH, with the consequent risk of irreversible visual loss, in patients without any ocular alterations before the diagnosis. Thus, there is a need for systematic and universal ophthalmological evaluation of children and adolescents with neoplasia in the lymphoid lineage from the very beginning of treatment.

CONCLUSION

Patients with ALL have elevated incidences of ocular manifestations due to the treatment and the disease itself. Among those, OH is the most prevalent. Patients treated with a protocol using higher doses of GC (ALL-99) and with high risk of recurrence had a higher risk of presenting ocular alterations, with strong association between those variables. Therefore, a protocol is proposed that contemplates systematic ophthalmological examination with the measurement of IOP immediately after diagnosis of ALL, before the introduction of GC (D0) and subsequently at D8, D28 and D6months.

REFERENCES

[1] Talcott KE, Garg RJ, Garg SJ. Ophthalmic manifestations of leukemia. *Current Opinion in Ophthalmology*2016; **27**: 545–551.

[2] Sharma T, Grewal J, Gupta S, Murray PI. Ophthalmic manifestations of acute leukaemias: the ophthalmologists role. *Eye*2004; **18**: 663–672.

[3] Reddy SC, Menon BS. A prospective study of ocular manifestations in childhood acute leukaemia. *Acta Ophthalmologica Scandinavica*1998; **76**: 700–703.

[4] Yalcinbayir O, Baytan B, Gelisken O, Can B, Evim MS, Yildiz M *et al.*Spectral domain optical coherence tomography findings of patients under treatment for pediatric acute lymphoblastic leukemia. *Journal of American Association for Pediatric Ophthalmology and Strabismus* 2017; **21**. doi:10.1016/j.jaapos.2016.12.002

[5] Çaça I, Ünlü K, Ari S, Dirier A. Unilateral Optic Disc Edema in a Patient With Acute Lymphocytic Leukemia: A Case and Review of the Literature. *Annals Of Ophthalmology*2005; **37**: 303–306.

[6] Chaudhuri T, Roy S, Roy P. Ischaemic optic neuropathy induced sudden blindness as an initial presentation of acute lymphoblastic leukemia. *Indian Journal of Medical and Paediatric Oncology*2013; **34**: 335.

[7] Gordon K. Ocular manifestations of leukemia leukemic infiltration versus infectious process. *Ophthalmology*2001; **108**: 2293–2300.

[8] Whelan KF, Stratton K, Kawashima T, Waterbor JW, Castleberry RP, Stovall M *et al.*Ocular late effects in childhood and adolescent cancer survivors: A report from the childhood cancer survivor study. *Pediatric Blood & Cancer*2010; **54**: 103–109.

[9] Mendonça CDQ, Souza CPD, Martins-Filho PRS, Viana SS, Leal BC, Cipolotti R. Steroid-induced ocular hypertensive response in children and adolescents with acute lymphoblastic leukemia and non-hodgkin lymphoma. *Pediatric Blood & Cancer*2014; **61**: 2083–2085.

[10] Fraunfelder F, Meyer SM. Ocular Toxicity of Antineoplastic Agents. *Ophthalmology*1983; **90**: 1–3.

[11] Cerdà-Ibáñez M, Bayo-Calduch P, Manfreda-Domínguez L, Duch-Samper A. Acute Vision Loss As The Only Sign Of Leukemia Relapse. *Retinal Cases & Brief Reports*2018; **12**: 10–11.

[12] Brandalise, S. R. et al. Benefits of the intermittent use of 6-mercaptopurine and methotrexate in maintenance treatment for low-risk acute lymphoblastic leukemia in children: randomized trial from the Brazilian Childhood Cooperative Group--protocol ALL-99. Journal of Clinical Oncology, v. 28, n. 11, p. 1911–1918, 10 abr. 2010.

[13] Curto ML, Zingone A, Acquaviva A, Bagnulo S, Calculli L, Cristiani L *et al.* Leukemic infiltration of the eye: Results of therapy in a retrospective multicentric study. *Medical and Pediatric Oncology*1989; **17**: 134–139.

[14] Russo V, Scott I, Querques G, Stella A, Barone A, Noci ND. Orbital and Ocular Manifestations of Acute Childhood Leukemia: Clinical and Statistical Analysis of 180 Patients. *European Journal of Ophthalmology*2008; **18**: 619–623.

[15] Khadka D, Sharma A, Shrestha JK, Shrestha GS, Shrestha PN, Pant SR *et al.*Ocular manifestations of childhood acute leukemia in a tertiiary level eye centre of Kathmandu, Nepal. *Nepalese Journal of Ophthalmology*2014; **6**. doi:10.3126/nepjoph.v6i2.11678.

[16] Bitirgen G, Belviranli S, Caliskan U, Tokgoz H, Ozkagnici A, Zengin N. Ophthalmic Manifestations in Recently Diagnosed Childhood Leukemia. *European Journal of Ophthalmology*2015; **26**: 88–91.

[17] Reddy S, Jackson N, Menon B. Ocular Involvement in Leukemia – A Study of 288 Cases. *Ophthalmologica*2003; **217**: 441–445.

[18] Schachat AP. Ophthalmic Manifestations of Leukemia. *Archives of Ophthalmology*1989; **107**: 697.

[19] Cogan DG. Immunosuppression and Eye Disease. *American Journal of Ophthalmology*1977; **83**: 777–788.

[20] Howard SC, Metzger ML, Wilimas JA, Quintana Y, Pui CH, Robison LL, Ribeiro RC. Childhood Cancer Epidemiology in Low-Income Countries. Cancer2008 Feb 1;112(3):461-72. Review.

5.2 Estudo de Reisão Sistemática (Artigo 2)

Steroid-Induced Ocular Hypertensive Response in Children and Adolescents with Acute Lymphoblastic Leukemia and Non-Hodgkin Lymphoma: a Systematic Review

(Artigo submetido no "Journal of Pediatric Hematology and Oncology JPHO-18-150. Foram submetidas as correções solicitadas pelos revisores; manuscrito com o Editor, aguardando parecer final).

Summary

The aim of this study was to conduct a systematic review to evaluate the risk of increased intraocular pressure (IOP) related to corticosteroids in children and adolescents with acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL). Eligible studies had to include children and adolescents up to 19 years of age with ALL or NHL, regardless of gender, and treated with systemic corticosteroids on a regular schedule. Four studies met the eligibility criteria: two were individual case reports, one a series of five cases and one observational prospective study of twelve patients. The results described eventual control of IOP, and outcomes ranging from no eye damage to total blindness. The possibility of silent

ocular hypertension, with consequent risk of irreversible blindness, indicates the need for evaluating the introduction of an IOP verification protocol in young patients immediately after diagnosis of ALL or NHL.

However, due to limited evidence, further studies on evaluation of IOP and visual function before starting treatment, as well as systematic measurements during and after treatment, are warranted.

Key words: ocular hypertension, steroids, acute lymphoblastic leukemia.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer during childhood, corresponding to 32% of neoplasms and 85% of all cases of childhood leukemia.[1] Non-Hodgkin lymphoma (NHL) accounts for approximately 4% of all malignancies among children.[2]

The first description of corticosteroid-induced ocular hypertension was published in 1950.3The disorder occurs independent of the method of drug administration and constitutes an important and preventable cause of visual loss. Previous studies had already shown that the risk of ocular hypertension is higher in children[4] especially after some weeks of corticosteroid administration, and that this is generally reversible with the suspension of the drug's use. However, if the ocular hypertension persists for a prolonged period, permanent damage of the optical nerve may occur, with consequent vision impairment.[5]

The aim of this study was to conduct a systematic review to evaluate the risk of increased intraocular pressure (IOP) and its possible implications for visual function related to corticosteroid therapy in children and adolescents with ALL and NHL.

Methods

A protocol of this systematic review was designed a priori and was registered in the PROSPERO database (registration number CRD42018087146).

Literature Search

We searched PubMed, Scopus, Web of Science, Science Direct, and Cochrane Library from inception to January 31, 2018. A grey-literature search was conducted through Google Scholar and OpenThesis. The first 100 results of Google Scholar were recorded. The search also included a hand search of cross-references from original articles and reviews. The structured search strategy used the following terms: (precursor cell lymphoblastic leukemia-

lymphoma OR acute lymphoblastic leukemia OR non-Hodgkin lymphoma) AND (glaucoma OR ocular hypertension). Two independent reviewers screened the search results and identified studies that were potentially relevant based on article titles and abstracts.
Relevant studies were read in full and selected according to the eligibility criteria.

Eligibility Criteria

In this systematic review, we included studies that reported the occurrence of corticosteroidinduced ocular hypertension in children and adolescents with ALL or NHL. Eligible studies had to include children and adolescents from 5 to 19 years of age, regardless of gender, and treated with systemic corticosteroids on a regular schedule for ALL or NHL. If the assessed study included several types of malignancies treated with systemic corticosteroid, separate data for ALL and NHL had to have been provided. Studies reporting ocular hypertension by tumoral infiltration, and glaucomatous field damage and outcome of corticosteroid-induced ocular hypertension at initial testing were excluded. We did not exclude any study on criteria of sample size, duration of follow-up, publication date, or language of publication.

Data Extraction

Two reviewers independently abstracted data from studies that met the eligibility criteria using apredefined coding protocol. Disagreements were resolved by consensus or, rarely, adjudication by a third reviewer. We extracted information on (1) design and demographic details, including type of study, number of patients, geographic location, type of malignancy, gender, age, treatment (chemotherapy, radiotherapy, or systemic corticosteroid use), previous ocular pathology, family history of glaucoma, diagnosis of corticosteroid-induced ocular hypertension, and standards for measurement of ocular pressure; (2) details of corticosteroid use and IOP, including data on induction and post-induction therapy (type of corticosteroid, course, and dosage), cycles, baseline IOP and values of ocular hypertension; (3) strategies to control IOP, including use of antiglaucoma medication, corticosteroid switching,
corticosteroid cessation, and complications.

Exposure and Outcome

The exposure was defined as treatment of ALL or NHL with systemic corticosteroids, regardless of type of corticosteroid or dosage. The outcome was the ocular hypertension occurring after the initiation of corticosteroid and defined as an IOP higher than 21 mmHg in one or both eyes.

Results

Altogether, 314 reports were retrieved and, after reviewing the titles and abstracts, 9 full-text articles were assessed for eligibility. Of these, 5 were excluded.6-10 The remaining 4 articles11-14 met the eligibility criteria and were included in the systematic review (Figure 1). The 4 reviewed articles11-14 were a case report in the form of a summary11, published for the American Society of Pediatric Hematology/Oncology 25th Annual Meeting, 2012, New Orleans,Louisiana; and 3 complete studies, designed as a case report12, a series of 5 cases13 and an observational prospective study with 12 patients.14 All included studies were published in the English language and the outcome under evaluation was the presence of ocular hypertension. No studies were multicenter or randomized.

The first study was presented as a poster at the American Society of Pediatric Hematology/Oncology 25th Annual Meeting, New Orleans, Louisiana, in 2012, by Pilbeam et al.11 The authors reported the case of a 3-year-old boy diagnosed with ALL, who had no previous history of visual problems or family history of glaucoma. On the 10th day of induction with dexamethasone 3 mg/m2, the patient presented with photophobia, irritability, decreased visual acuity and dilated pupils. The initial diagnostic hypothesis was optic neuropathy, but the brain magnetic resonance and angioresonance were normal. Ocular exam showed visual acuity at 20/200, dilated non-reactive pupils and elevated IOP (OD 42 mmHg, OS 40 mmHg). The patient, although treated for glaucoma, developed permanent blindness in the right eye and a significant loss of vision in the left eye.

In the second study, Tham et al.12 reported the case of a 9-year-old-girl with ALL who received high doses of systemic corticosteroid (60 mg daily of oral prednisolone) and presented on the 10th day of treatment an IOP of 52 mmHg in the right eye and 47 mmHg in the left eye. Topical medications to treat glaucoma were used (latanoprost 0.001% once daily and brimonidine 0.2% twice daily) and the pressure dropped to 38 mmHg and 36 mmHg. IOP returned to baseline after 2 days of suspension of the corticosteroid and after 6 weeks of follow-up, this level was maintained even without glaucoma

medications. Four months later, the patient was submitted to a new cycle of treatment with 10 mg of oral dexamethasone daily. The patient showed similar increase in IOP for both eyes

during the course of oral dexamethasone. Oral acetazolamide was prescribed and the patient remained asymptomatic throughout treatment, except for one episode of decreased visual acuity in the right eye when IOP reached 52 mmHg.

In the third study, Yamashita et al.13 reported a case series including children up to 6 years of age diagnosed with ALL (2 boys and 3 girls, mean 4.2 ± 1.6 years). The 15 treatment cycles were each composed of induction therapy (prednisolone 60 mg/m2/day for 4 weeks) followed by late intensification therapy (dexamethasone 6mg/m2/day for 2 weeks) and a maintenance regime (dexamethasone,6mg/m2/day for 2 weeks, then 1 week of tapering and a 5-week break). The patients with ocular symptoms were referred to an ophthalmologist throughout the treatment. Children were examined for visual acuity and IOP was measured by non-contact tonometry (CT-80, Topcon, Japan) on each 7th day of induction therapy and 7th day of maintenance regime. All patients had IOP above 21 mmHg, with a mean of 39.6 ± 7.2 mmHg (range 28 to 47). Antiglaucoma medication was given to all presenting IOP above 25 mmHg. Of the 5 patients included in this study, one received only antiglaucoma medication; 3 were treated with antiglaucoma medication and the steroid switched from dexamethasone to prednisolone; and one showed a well-controlled IOP with antiglaucoma medication and cessation of corticosteroid therapy, even though he presented severe glaucomatous optic atrophy. In all cases, regardless of the method of IOP control, the pressure was normalized.

In the most recent study included in this review, Mendonca et al.14 performed a prospective observational study with measurement of IOP before treatment (D0), and on the 8th (D8), 14th (D14), and 28th days (D28) of treatment. The authors examined 12 patients (mean age of 8.8 ± 5.4 years), 11diagnosed with ALL and one with NHL. Eight patients were given prednisone and 4 received dexamethasone. Two cases (16.7%) of ocular hypertension were observed, the first induced by dexamethasone with IOP at 42 mmHg in both eyes on D14, and the second case induced by prednisone with IOP at 26 mmHg in both eyes on D8. Satisfactory control of the IOP was obtained using eye drops of Brinzolamide 1.0% and timolol maleate 0.5 % twice a day. No patient presented ocular hypertension after D28, when the corticosteroids were suspended. Differences of IOP between D0 vs. D8 and D0 vs. D14 ($p=0.013$) were observed. The results of this review are summarized in Tables 1 and 2.

Discussion

This systematic review included 9 children who were diagnosed with ALL and presented steroidinduced ocular hypertension. No cases in children with NHL were reported.

Unfortunately, although we used an explicit method to identify and select relevant studies, a limited number were found for inclusion.

Only one study among those 4 that met the eligibility criteria had been prospective14 and had estimated the incidence of the steroid-induced ocular hypertension in a sample of 12 children.

The increased risk of steroid-induced ocular hypertension remains controversial. Recently, Whelan et al[6] in a multi-institutional collaborative study of individuals who survived at least 5 years after 7 diagnosis of cancer during childhood or adolescence, did not find an increased risk of glaucoma among survivors treated with glucocorticoid therapy. However, the authors suggest that the true incidence of ocular hypertension may be underestimated, since patients can remain asymptomatic, that regular eye exams and additional follow-up may uncover increased risk of glaucoma in childhood cancer survivors treated with corticosteroids and that it is also important that IOP be measured at the beginning of corticosteroid therapy, making it possible to evaluate the real increase in pressure levels and the ideal reading to indicate their control. Of the 4 studies included in this review, only 2 studies12,14 reported the measurement of ocular pressure at the beginning of corticosteroid treatment.

The use of varied methods to measure IOP can also explain differences in the incidence of ocular hypertension in children receiving corticosteroid therapy. In the study performed by Yamashita et al.13, IOP was measured by air puff, non-contact tonometry (Topcon CT-80) that does not have the reliability of contact tonometry, resulting in possible overestimation of values in children. Pediatric patients with ALL or NHL receiving corticosteroid can remain asymptomatic in spite of severe ocular hypertension.

Thus, controlled studies with evaluation of IOP by applanation tonometry become necessary in order to insure more precise diagnoses and treatment decisions, as shown by Mendonca et al.[14]

All patients diagnosed with steroid-induced ocular hypertension included in this study were treated with ocular hypotensive medications with adequate control of IOP in most cases. However, some serious complications were observed in the studies by Pilbeam et al.11, Tham et al.[12], and Yamashita et al.[13],including severe glaucomatous optic atrophy and permanent blindness. According to Tham et al.[12], the most effective way to normalize the IOP appeared to be cessation of the corticosteroid therapy, but this conduct is impossible in most cases due to the nature of the underlying medical condition. In the study performed by Yamashita et al.[11], different methods were used to control the IOP, but all of them included the use of antiglaucoma medications. The use of ocular hypotensive medications thus appears to be an

adequate choice for the control of steroid-induced ocular hypertension in children, whether the type of steroid is switched or not. However, further studies are needed to verify the best combination therapy in the treatment of steroid-induced ocular hypertension in pediatric patients with ALL and NHL.

In this review, only the study performed by Mendonca et al.[14] showed measurements of IOP and visual function at the beginning of corticoid induction, as well as systematic measurements during and after the treatment. The authors observed a significant increase of IOP compared to baseline during the remission induction phase of treatment, when elevated doses of glucocorticosteroids were used. In 2 out of 12 patients (16.7%), the IOP levels could have been high enough to cause glaucomatous optic neuropathy and eventually blindness, since the risk of glaucomatous nerve damage is directly related to the level and duration of IOP.[11,15]

Conclusion

The possibility of silent ocular hypertension, with consequent risk of irreversible blindness, indicates the need for evaluating the introduction of an IOP verification protocol in young patients immediately after diagnosis of ALL or NHL. However, due to limited evidence, further studies on evaluation of IOP and visual function before starting treatment, as well as systematic measurements during and after treatment, are warranted.

Figure 1 **Flow diagram**.

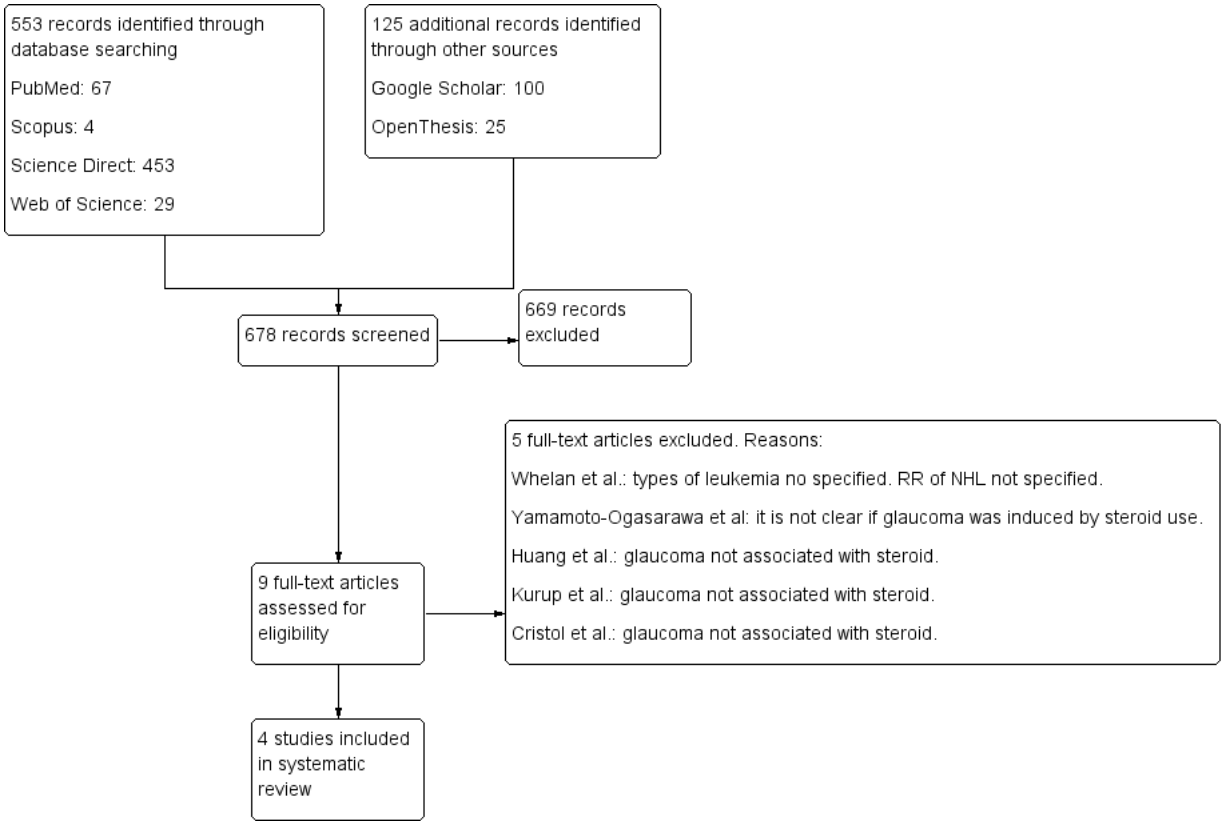

Table 1. Design features and demographic details of studies included in the systematic review.

Study	Type of study	Number of patients	Country	Malignancy	Sex	Age	Treatment			SIOH	Measurement
							CT	RT	Oral GC		
Mendonca et al. [14]	Prospective observational	12	Brazil	ALL and NHL	5F:7M	8.8y (mean)	Yes	No	Yes	2 patients	Perkins applanation tonometry
Yamashita et al.[13]	Case series	5	Japan	ALL	3F:2M	4.2y (mean)	Yes	No	Yes	All patients	Noncontact tonometry (CT-80, TOPCON)
Tham et al.[12]	Case report	1	China	ALL	F	9y	ND	ND	Yes	Yes	Goldmann applanation tonometry
Pilbeam et al.[11]	Case report	1	USA	ALL	M	3y	Yes	No	Yes	Yes	ND

CT: chemotherapy; RT: radiotherapy; ND: not described; SIOH: steroid-induced ocular hypertension.

Table 2. IOP control and complications in patients with steroid-induce ocular hypertension.

Study	Patient	Method			IOP	Complications
		Antiglaucoma medication	Steroid switching	Steroid cessation		
Mendonca et al.[14]	1	Yes	No	No	Well controlled	No
	2	Yes	No	No	Well controlled	No
Yamashita et al.[13]	3	Yes	Yes	No	Well controlled	No
	4	Yes	No	No	Well controlled	No
	5	Yes	Yes	No	Well controlled	No
	6	Yes	No	Yes	Well controlled	Severe glaucomatous optic atrophy and decrease of retinal nerve fibers layer thickness
	7	Yes	Yes	No	Well controlled	No
Tham et al.[12]	8	Yes	No	No	Poorly controlled	One episode of decreased visual acuity
Pilbeam et al.[11]	9	Yes	No	No	Poorly controlled	Permanent blindness in the right eye and significant vision loss in the left eye

References

1. Yasmeen N, Ashraf S. Childhood acute lymphoblastic leukaemia; epidemiology and clinicopathological features. J Pak Med Assoc. 2009;59(3):150–153.

2. Alexander DD, Mink PJ, Adami HO, et al. The non-Hodgkin lymphomas: A review of the epidemiologic literature. Int J Cancer. 2007;120(S12):1–39.

3. McLean JM. Use of ACTH and cortisone.Trans Am Ophthalmol Soc.1950; 48:293-296.

4. Brito P, Silva S, Cotta J, Falcão-Reis F. Severe ocular hypertension secondary to steroid treatment in a child with nephrotic syndrome. Clin Ophthalmol.2012; 6:1675-9.

5. Danias J, Gerometta R, Ge Y, et al. Gene expression changes in steroid-induced IOP elevation in bovine trabecular meshwork. Invest Ophthalmol Vis Sci. 2011;52(12):8636–8645.

6. Whelan KF, Stratton K, Kawashima T, et al. Ocular late effects in childhood and adolescent cancer survivors: a report from the childhood cancer survivor study. Pediatr Blood Cancer. 2010;54(1):103–109.

7. Yamamoto-Ogasawara A, Asakawa M, Yoshino K, Nagamoto T, Inoue M, Hirakata A. Anterior complications in case of recurrent acute lymphoblastic leukaemia diagnosed by biopsy of aqueous humour. Clin Exp Ophthalmol. 2009;37(7):739–741.
8. Huang LT, Hsiao CC, Weng HH, Lui CC. Neurologic complications of pediatric systemic malignancies. J Formos Med Assoc. 1996;95(3):209–212.
9. Kurup SK, Levy-Clarke G, Calvo KR, Jaffe ES, Nussenblatt RB, Chan C-C. Primary diffuse large B-cell lymphoma of the spleen with coincident serous retinal detachments responsive to corticosteroids. Clin Exp Ophthalmol. 2007;35(5):468–472.
10. Cristol SM, Baumblatt JG, Icasiano E, Grajewski AL, Olivier MMG, Parrish RK. Bilateral acute angle-closure associated with systemic lymphoma: a report of 2 cases. J Glaucoma. 2011;20(2):115–117.
11. Pilbeam K, Salvi S, Havani A. Corticosteroid-induced glaucoma as a complication of induction therapy in a child with acute lymphoblastic leukemia (ALL). ASPHO Abstracts. Pediatr Blood Cancer. 2012; 58:1014-1097.
12. Tham C, Ng J, Li R, Chik KW. IOP profile of a child on a systemic corticosteroid. Am J Ophthalmol. 2004; 137(1): 198-201.
13. Yamashita T, Kodama Y, Tanaka M, Yamakiri K, Kawano Y, Sakamoto T. Steroid-induced glaucoma in children with acute lymphoblastic leukemia: a possible complication. J Glaucoma. 2010;19(3):188–190.
14. Mendonca C, de Souza CP, Martins-Filho PRS, Viana SS, Leal BC, Cipolotti R. Steroid-induced ocular hypertensive response in children and adolescents with acute lymphoblastic leukemia and non-Hodgkin lymphoma. Pediatr Blood Cancer. 2014;61(11):2083–2085.
15. Bresson-Dumont H. IOP in children. J Fr Ophtalmol.2009; Mar.32(3):176-81

5.3 Regras para Publicação

5.3.1 Estudo de Coorte (Artigo 1)

Description

Author Information Pack

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Leukemia Research an international journal which brings comprehensive and current information to all health care professionals involved in basic and applied clinical research in hematological malignancies. The editors encourage the submission of articles relevant to hematological malignancies. The Journal scope includes reporting studies of cellular and molecular biology, genetics, immunology, epidemiology, clinical evaluation, and therapy of these diseases.

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[4] G.R. Mettam, L.B. Adams, How to prepare an electronic version of your article, in: B.S. Jones, R.Z. Smith (Eds.), Introduction to the Electronic Age, E-Publishing Inc., New York, 2009, pp. 281–304. Reference to a website:
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Journal Of Pediatric Hematology And Oncology

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Journal Article

1. Ang KK, Price RE, Stephens LC, et al. The tolerance of primate spinal cord to re-irradiation. Int J Radiat Oncol Biol Phys. 1993;25:459–464.

Book Chapter

2. Dimery IW. Chemotherapy in head and neck cancer. In: Myerhoff WI, Rice DH, eds. Otolaryngology: head and neck surgery, 2nd ed. Philadelphia: WB Saunders, 1992:1027–1045.

Entire Book

3. Virchow R. Cellular Pathology. Philadelphia: JB Lippincott, 1863.

Software

4. Epi Info [computer program]. Version 6. Atlanta, GA: Centers for Disease Control and Prevention; 1994.

Online Journals

5. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database

6. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web

7. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS Web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

URL (Uniform Resource Locator)

8. (J. M. Kramer, K. Kramer [jmkramer@umich.edu], e-mail, March 6, 1996).

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6 DISCUSSÃO GERAL

A associação entre MO em pacientes pediátricos portadores de LLA está escassamente contemplada na literatura. De maneira geral, a fisiopatologia do acometimento ocular na LLA deve-se a três mecanismos principais: I) infiltração direta do olho e órbita pelas células neoplásicas; II) anormalidades vasculares afetando a retina ou III) acometimento neuro-oftalmológico (REDDY; MENON, 1998). Não podemos ignorar ainda, os efeitos dos quimioterápicos na visão dos pacientes. O uso de altas doses de GC no tratamento desses pacientes, por si só, já implica em um risco significativamente aumentado de desenvolver, por exemplo, HO, catarata, glaucoma cortisônico, olho seco, diplopia e cegueira (MENDONCA et al., 2014; WHELAN et al., 2010), que pode persistir em alguns casos, cessado o seu uso.

O primeiro artigo apresenta os resultados da primeira investigação com delineamento prospectivo em um estudo de coorte prospectivo em crianças e adolescentes com LLA, em um serviço público especializado em oncologia pediátrica localizado na região nordeste do Brasil entre 1º de janeiro de 2013 e 30 de dezembro de 2017. O diferencial em relação aos estudos anteriores foi a realização de exame oftalmológico em D0, D8, D28 e D6meses. Os resultados foram apresentados de maneira descritiva e avaliando se as MO podem estar associadas a fatores de risco para recaída da doença, tipo de uso de protocolo de tratamento, gênero, idade, imunofenotipagem, óbito e infiltração liquórica.

De um total de 78 pacientes admitidos no serviço entre 2013 e 2017, 67 preencheram os critérios de inclusão, porém 12 deles foram a óbito antes do D8. Cinquenta e cinco tiveram exame ocular realizado pelo menos uma vez entre o D8 e o D6meses. Destes, foram obtidos dois grupos: pacientes com exame normal (N=37) e pacientes que apresentaram alguma manifestação ocular (N=18). O presente estudo identificou 33% de pacientes com comprometimento ocular em alguma etapa do tratamento, contrastando com alguns resultados de estudos anteriores que obtiveram 15-39%, divergência que reflete a aplicação de diferentes métodos. Adicionalmente, no presente estudo, a maior proporção de alterações oculares se deve à inclusão dos casos de HO, que foram ativamente rastreados nessa coorte, mesmo na ausência de sintomas. Tiveram MO estatisticamente significativas os pacientes de alto risco para recaída, compatível com o descrito na literatura (RUSSO et al., 2008) e os pacientes tratados com protocolo de 1999, o que pode ser explicado pela dose total de GC, que é maior que a do protocolo de 2009 (BRANDALISE et al., 2010; WATANABE, 2007).

Envolvimento ocular direto ocorreu em um paciente (2%) sob a forma de infiltração leucêmica do nervo óptico, alteração observada em 7,3% dos casos em estudo anterior (KHADKA et al., 2014). Entre as alterações oftálmicas secundárias, a retina foi o tecido mais

afetado, ocorrendo hemorragia em 7,3% dos casos, proporção consistentemente semelhante ao descrito anteriormente: 8 - 8,8% (BITIRGEN et al., 2016; REDDY; MENON, 1998).

Outras alterações secundárias foram o desenvolvimento de celulite orbitária (2%) e uveíte devido a Herpes zoster (2%). Pacientes com LLA podem adquirir infecções por germes oportunistas e reativar infecções virais durante os períodos de neutropenia, com elevado risco de morte (COGAN, 1977).

Observou-se que, durante a fase de indução da remissão, quando doses elevadas de corticosteroides são utilizadas, houve aumento significativo da PIO em dez pacientes (20%), cujos valores foram compatíveis com HO (PIO> 21mmHg). O resultado foi superior ao apresentado em estudo anterior, que obteve 16,6% (MENDONCA et al., 2014). Houve diferença estatisticamente significativa na variação da PIO em aferições realizadas durante a fase de indução da remissão, entre D8 e D6meses (p=0,026). Esse achado representa o padrão de variação de PIO observado no glaucoma cortisônico (KERSEY; BROADWAY, 2005).

Inicialmente, a PIO aumentou consideravelmente, mas os valores pressóricos já estavam normalizados no D28 e D6meses, seja com a utilização do tratamento antiglaucomatoso (quando os valores de PIO eram compatíveis com HO), seja com o término da utilização de GC no final do tratamento. No glaucoma induzido por GC a elevação da PIO é gradual e progressiva. Então, assim como no glaucoma de ângulo aberto, os sintomas são pouco evidentes, mesmo com risco de danos às fibras nervosas ópticas (KHADKA et al., 2014). Como em estudos anteriores (COGAN, 1977; CURTO et al., 1989; KHADKA et al., 2014; MENDONCA et al., 2014; REDDY; MENON, 1998; RUSSO, 2008), neste estudo nenhum paciente com HO isolada desenvolveu sintomas, o que dificulta o diagnóstico quando não é feito o rastreamento sistemático de todos os pacientes, independentemente da existência de sintomas.

Houve quatro pacientes com BAV definitiva (7,3%), nenhum deles com HO isolada. Somente os pacientes com outras alterações secundárias da doença como hemorragia retiniana, palidez do nervo óptico, infiltração leucêmicas e uveíte evoluíram com BAV.

Assim, existe a possibilidade de MO e HO silenciosa, com o consequente risco de dano irreversível em pacientes sem alterações oculares no início do tratamento. Os pacientes classificados com AR para recidiva da doença no momento do diagnóstico e que fizeram uso do protocolo de tratamento ALL-99 foram os que mais apresentaram MO.

Devido à alta prevalência de HO encontrada no estudo da coorte, foi feito um estudo de revisão sistemática da literatura para avaliar a relação entre HO e Glaucoma em pacientes pediátricos tratados para LLA, devido ser a MO mais prevalente. Foram encontrados quatro

artigos: dois relatos de casos (PILBEAM; SALVI; HAVANI et al., 2012; THAM et al., 2004), uma série de cinco casos (YAMASHITA et al., 2010) e um estudo descritivo prospectivo de 12 pacientes (MENDONÇA et al., 2014). Foram diagnosticadas nove crianças com HO.

O primeiro estudo foi apresentado por Tham e colaboradores em 2004 relatando um caso de HO em paciente tratado para LLA, cuja PIO variou de 16 a 17 mmHg antes do uso de GC, até 52 mmHg em OD e 47 mmHg no OE no décimo dia de tratamento. Esse paciente recebeu doses elevadas de GC sistêmico e, apesar do tratamento com medicações tópicas, só houve retorno para níveis após dois dias de suspensão desta medicação. Após novo ciclo de tratamento com GC oral (dexametasona) o paciente apresentou o mesmo comportamento da PIO, com o retorno aos níveis básicos somente com a interrupção da dexametasona (THAM et al., 2004). Esse relato de caso exemplifica a real fisiopatologia da HO induzida pelo GC, caracterizada pelo retorno a níveis de PIO normais após suspensão do GC (ZHANG; CLARK; YORIO, 2005).

Yamashita et al. (2010) relataram uma série retrospectiva de casos envolvendo crianças de até seis anos de idade portadoras de LLA. Eles foram tratados com prednisolona, 60 mg/m^2/dia na fase de indução da remissão, e dexametasona 6 mg/m^2/dia na fase de manutenção. Todos os pacientes tiveram a pressão ocular acima de 21 mmHg e foram tratados com medicações para diminuir níveis pressóricos oculares. No final, após suspensão do GC, nenhum dos pacientes necessitou de medicações para diminuir a PIO. Um deles apresentou atrofia óptica glaucomatosa, diminuição da espessura das fibras nervosas da retina (confirmado pelo OCT), apesar de se ter obtido o controle da PIO. Nesse estudo, os cinco pacientes foram encaminhados para um oftalmologista por causa de seus sintomas oculares (YAMASHITA et al., 2010). A forma em que foi aferida a PIO, por sopro de ar ou por tonometria de não-contato, não tem a previsibilidade da tonometria de contato, resultando em possível superestimação dos valores em crianças (BRESSON-DUMONT, 2009). Este fato pode explicar o achado de HO em todos os pacientes desse estudo. Devido a estes resultados controversos, estudos controlados com medição da PIO por tonometria de aplanação se fazem necessários a fim de garantir diagnósticos mais precisos. Todos os pacientes receberam medicação contra o glaucoma, um achado oposto aos resultados da coorte *Childhood Cancer Survivor Study* (CCSS), que refere como não estatisticamente significante a possibilidade de glaucoma em crianças após cinco ou mais anos de tratadas para câncer (WHELAN et al., 2010). Possivelmente essa diferença ocorreu por superestimação dos valores da PIO, bem

como pelas particularidades de amostragem, uma vez que todos os pacientes apresentaram sintomas oculares.

Outro relato de caso foi apresentado por Pilbeam, Salvi e Havani em 2012, que avaliaram um menino de três anos de idade com diagnóstico de LLA e que no décimo dia de indução com dexametasona 3 mg/m^2, apresentou fotofobia, irritabilidade, diminuição da acuidade visual e pupilas dilatadas. O exame ocular mostrou acuidade visual em 20/100 e PIO elevada (OD 42 mmHg, OE 40 mmHg). Apesar de o tratamento para o glaucoma, o paciente apresentou cegueira permanente em OD e perda significativa de visão em OE (PILBEAM; SALVI; HAVANI, 2012).

É importante ressaltar que nos estudos citados (PILBEAM; SALVI; HAVANI, 2012; YAMASHITA et al., 2010) não houve aferição da PIO antes do tratamento com GC, o que torna impossível avaliar o aumento real dos níveis pressóricos e qual seria o controle ideal da PIO. A PIO foi aferida antes do tratamento apenas em um artigo publicado (THAM et al., 2004).

Os resultados finais descritos na literatura são divergentes quanto ao controle da PIO. Embora os pacientes descritos por Yamashita e colaboradores (2010) tenham apresentado um bom controle de PIO, houve perda de fibras nervosas da retina em um paciente. No relato de Tham e colaboradores (2004) o controle da PIO foi insuficiente para manter-se em níveis adequados durante a terapia de indução. Embora os dados sobre o controle da PIO não tenham sido descritos no estudo, o paciente evoluiu com cegueira permanente no olho direito e perda importante da visão no olho esquerdo, caracterizando o efeito deletério do GC sobre a função visual (PILBEAM; SALVI; HAVANI, 2012).

Apenas o estudo realizado por Mendonca e colaboradores (2014) mostrou medidas de PIO e da função visual no início da indução de GC, bem como medidas sistemáticas durante e após o tratamento. Os autores observaram um aumento significativo da PIO em relação ao valor basal durante a fase de indução da remissão (primeiros 28 dias de tratamento), quando doses elevadas de GC foram utilizadas. Em dois de 12 pacientes (16,7%), os níveis de PIO poderiam ter sido altos o suficiente para causar neuropatia óptica glaucomatosa e, eventualmente, cegueira, uma vez que o risco de lesão do nervo glaucomatoso está diretamente relacionado ao nível e a duração da PIO.

Os autores sugerem que a verdadeira incidência de HO pode estar subestimada, uma vez que os pacientes podem permanecer assintomáticos. Exames oftalmológicos regulares e acompanhamento adicional podem revelar risco aumentado de glaucoma em sobreviventes de câncer infantil tratados com GC, e também é importante que a PIO seja medida no início da

corticoterapia, possibilitando avaliar o aumento real dos níveis pressóricos e a leitura ideal para indicar seu controle.

Assim, existe a possibilidade de HO silenciosa, com o consequente risco de dano irreversível em pacientes sem alterações oculares no início do tratamento. Identifica-se assim a necessidade de avaliação oftalmológica sistemática e universal em crianças e adolescentes com LLA desde o início do tratamento. Propõe-se a introdução de um protocolo que contemple exame oftalmológico sistemático, incluindo aferição da PIO imediatamente após o diagnóstico de LLA e antes da introdução de GC, prosseguindo-se em D8, D28 e D6meses.

7 CONCLUSÃO

Os pacientes estudados com LLA são jovens, com elevada expectativa de vida, pouca ou nenhuma comorbidade, e possuem doença oncológica com elevado potencial de cura. Apresentam uma alta incidência de MO devido ao tratamento e à própria doença, podendo ser assintomáticos e até evoluírem com BAV. Aqueles classificados com AR para recidiva da doença no momento do diagnóstico e os submetidos ao protocolo de 1999 são os mais propensos a apresentar MO e essas variáveis estão fortemente associadas. A HO é a MO de maior prevalência. Poucos estudos foram encontrados correlacionando crianças com LLA e HO, com resultados variando de HO silenciosa, sem alterações visuais, até cegueira irreversível.

Portanto, é proposto um protocolo que contemple exame oftalmológico geral, incluindo a medida da PIO, imediatamente após o diagnóstico de LLA (D0) e, posteriormente, em D8, D28 e D6meses. A necessidade do exame oftalmológico após os seis primeiros meses de tratamento deve ser avaliada a partir de então. Estudos clínicos controlados futuros poderão determinar a periodicidade e quais os exames oftalmológicos após D6meses.

7.1 Conclusão dos Artigos

7.1.1 Estudo de Coorte (Artigo 1)

“Manifestações Oculares em pacientes pediátricos com Leucemia Linfoblástica Aguda: Uma coorte de 5 anos”.

Objetivo específico 2:

- Identificar precocemente possíveis MO em pacientes pediátricos com LLA.
- Correlacionar se fatores prognósticos estabelecidos para recidiva de doença oncológica (tipo de protocolo de tratamento quimioterápico utilizado, gênero e infiltração do líquor por células neoplásicas) podem predizer risco a desenvolver MO (artigo 1).

Conclusão:

a) A amostra estudada revela possibilidade de ocorrer MO em pacientes pediátricos portadores de LLA.
b) O presente estudo identificou 33% de pacientes com MO em alguma etapa durante os seis primeiros meses de tratamento.
c) Aqueles submetidos ao protocolo de 1999 são os que apresentam maior risco de desenvolver MO.
d) A HO foi a alteração ocular mais prevalente (20%). Os níveis pressóricos oculares podem atingir níveis compatíveis para perda de fibras nervosas retiniana.
e) O tratamento precoce das MO pode prevenir em alguns casos perdas visuais.
f) Houve quatro pacientes com BAV definitiva (7,3%), nenhum deles com HO isolada.
g) A introdução de um protocolo de avaliação oftalmológica incluindo aferição sistemática de PIO faz-se necessário, devido a possibilidade de alterações oculares, com o consequente risco de cegueira irreversível.

7.1.2 Estudo de Revisão Sistemática (Artigo 2)

Steroid-Induced Ocular Hypertensive Response in Children and Adolescents with Acute Lymphoblastic Leukemia and Non-Hodgkin Lymphoma: Systematic Review.

Objetivo específico 1:

- Descrever a produção científica nacional e internacional em forma de Revisão Sistemática da MO com maior prevalência, a HO.

Conclusão:

a) Poucos estudos específicos sobre o assunto descritos na literatura, limitando-se a dois relatos de casos, outra série de cinco pacientes e apenas um estudo descritivo, prospectivo e sistemático de 12 casos.
b) Os resultados variaram de HO silenciosa, sem alterações visuais, até cegueira irreversível.
c) A verdadeira incidência de HO pode estar subestimada devido a poucos estudos prospectivos controlados na literatura científica.
d) Faz-se necessária a realização de estudos controlados, com medidas da PIO antes do início do GC, bem como de medidas seriadas padronizadas durante e após o tratamento.

REFERÊNCIAS

ADHIKARY, H. P.; SELLS, R. A.; BASU, P. K. Ocular complications of systemic steroid after renal transplantation and their association with HLA. **The British journal of ophthalmology**, v. 66, n. 5, p. 290–291, 1 May 1982.

ALEMAYEHU, W.; SHAMEBO, M.; BEDRI, A. et al. Ocular manifestations of leukaemia in Ethiopians. **Ethiop Med J,** v. 34, p. 217–224, 1996.

ALLEMANI, C.; WEIR, H. K.; CARREIRA, H. et al. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). **The Lancet,** [s.l.], v. 385, n. 9972, p. 977-1010, Mar. 2015. Elsevier BV. http://dx.doi.org/10.1016/s0140-6736(14)62038-9.

ALLEN, R. A.; STRAATSMA, B. R. Ocular involvement in leukaemia and allied disorders. **Arch Ophthalmol,** v. 66, p. 490–508, 1961.

APONTE, E. P.; DIEHL, N.; MOHNEY, B. G. Incidence and clinical characteristics of childhood glaucoma: a population-based study. **Archives of ophthalmology**, v. 128, n. 4, p. 478–482, 2010.

ARMALY, M. F.; BECKER, B. Intraocular pressure response to topical corticosteroids. **Federation proceedings**, v. 24, n. 6, p. 1274–1278, 1 nov. 1965.

BALLANTYNE, A. J.; MICHAELSON, I. C. **Textbook of the Fundus of the Eye**. Williams and Wilkins: Baltimore, 1970. p. 290–292.

BERBIS, J.; MICHEL, G.; BARUCHEL, A. et al. Cohort Profile: The French Childhood Cancer Survivor Study For Leukaemia (LEA Cohort). **International Journal Of Epidemiology,** [s.l.], v. 44, n. 1, p.49-57, 17 Mar. 2014. Oxford University Press (OUP). http://dx.doi.org/10.1093/ije/dyu031.

BITIRGEN, G. ; BELVIRANLI, S. ; CALISKAN, U. et al. Ophthalmic manifestations in recently diagnosed childhooh leukemia. **Eur J Ophthalmol**., v. 26, n. 1, p. 88-91, Jan./Feb. 2016.

BRANDALISE, S. R. ; PINHEURO, V. R. ; AGUIAR, S. S. et al. Benefits of the intermittent use of 6-mercaptopurine and methotrexate in maintenance treatment for low-risk acute lymphoblastic leukemia in children: randomized trial from the Brazilian Childhood Cooperative Group--protocol ALL-99. **Journal of Clinical Oncology**, v. 28, n. 11, p. 1911–1918, 10 Apr. 2010.

BRESSON-DUMONT, H. Intraocular pressure measurement in children. **J Fr Ophtalmol**., v. 32, n. 3, p. 176-181, Mar. 2009.

BRITO, P.; SILVA, S. E.; COTTA, J. S. et al. Severe ocular hypertension secondary to systemic corticosteroid treatment in a child with nephrotic syndrome. **Clinical Ophthalmology,** [s.l.], p.1675-1679, Oct. 2012. Dove Medical Press Ltda. http://dx.doi.org/10.2147/opth.s36261.

ÇAÇA, I. ; ÜNLÜ, K. ; ARI, S. et al. Unilateral Optic Disc Edema in a Patient With Acute Lymphocytic Leukemia: A Case and Review of the Literature. **Annals Of Ophthalmology,** [s.l.], v. 37, n. 4, p.303-306, 2005. Springer Nature. http://dx.doi.org/10.1385/ao:37:4:303.

CAVDAR, A. O.; GOZDASOGLU, S.; ARCASOY, A. et al. Chloroma-like ocular manifestations in Turkish children with acute myelo-monocytic leukaemia. **Lancet**, v. 1, p. 680–682, 1971.

CERDÀ-IBÁÑEZ, M.; BAYO-CALDUCH, P.; MANFREDA-DOMÍNGUEZ, L. et al. Acute Vision Loss As The Only Sign Of Leukemia Relapse. **Retinal Cases & Brief Reports**, v. 12, p. 10–11, 2018.

CHARIF, C. M.; BELMEKKI, M.; HAJJI, Z. et al. Ophthalmic manifestations of acute leukemia. **J Fr Ophtal**- mol, v. 25, n. 1, p. 62-66, 2002.

CHAUDHURI, T.; ROY, S.; ROY, P. Ischaemic optic neuropathy induced sudden blindness as an initial presentation of acute lymphoblastic leukemia. **Indian Journal Of Medical And Paediatric Oncology,** [s.l.], v. 34, n. 4, p. 335-335, 2013. Medknow. http://dx.doi.org/10.4103/0971-5851.125266.

CLAES, K.; KESTELYN, P. Ocular manifestations of graft versus host disease following bone marrow transplantation. **Bull Soc Belge Ophtalmol,** v. 77, p. 21–26, 2000.

CLARK, A. F.; WORDINGER, R. J. The role of steroids in outflow resistance. **Experimental Eye Research,** [s.l.], v. 88, n. 4, p.752-759, Apr. 2009. Elsevier BV. http://dx.doi.org/10.1016/j.exer.2008.10.004

COGAN, D. G. Immunosuppression and eye disease. **Am J Ophthalmol,** v. 83, p. 777–788, 1977.

COLOMBINI, A.; BARZAGHI, A.; CASTAGNETO, M. et al. Retro-orbital late relapse in a child with leukaemia after allogeneic bone marrow transplantation. **Acta Haematol,** v. 94, p. 44–47, 1995.

CULLIS, C. M.; HINES, D. R.; BULLOCK, J. D. Anterior segment ischaemia: classification and description in chronic myeloid leukaemia. **Ann Ophthalmol**, v. 11, p. 1739–1744, 1979.

CURTO, M. L. O.; ZINGONE, A.; AQUAVIVA, A. et al. Leukaemic infiltration of the eye: results of therapy in a retrospective multicentric study. **Med Pediatr Oncol,** v. 17, p. 134–139, 1989.

DANIAS, J.; GEROMETTA, R.; GE, Y. et al. Gene Expression Changes in Steroid-Induced IOP Elevation in Bovine Trabecular Meshwork. **Investigative Opthalmology & Visual**

Science, [s.l.], v. 52, n. 12, p.8636-8645, 7 nov. 2011. Association for Research in Vision and Ophthalmology (ARVO). http://dx.doi.org/10.1167/iovs.11-7563.

DAWSON, D. M.; ROSENTHAL, D. S.; MOLONEY, W. C. Neurologic complications of acute leukaemia in adults: changing rates. **Ann Int Med,** v. 79, p. 541–544, 1973.

DE CAMARGO, B.; DE OLIVEIRA SANTOS, M.; REBELO, M. S. et al. Cancer incidenceamong children and adolescents in Brazil: first report of 14 population-based cancer registries. **Int J Cancer**, v. 126, p. 715–720, 2010.

DUKE-ELDER, S. System of ophthalmology. **Cornea and conjunctiva**. CV Mosby: St Louis, 1965. p. 1190–1195. Vol V111.

ESSIG, S.; LI, Q.; CHEN, Y. et al. Risk of late effects of treatment in children newly diagnosed with standard-risk acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study cohort. **The Lancet Oncology,** [s.l.], v. 15, n. 8, p. 841-851, July 2014. Elsevier BV. http://dx.doi.org/10.1016/s1470-2045(14)70265-7.

GIAGOUNIDIS, A. A.; MECKENSTOCK, G.; FLACKE, S. et al. Ocular changes in renal transplant patients. **American journal of ophthalmology,** v. 63, n. 2, p. 283–289, 1 fev. 1967.

GOLDMANN, H.; SCHMIDT, T. Über Applanations tonometrie. **Oph- thalmologica**, v. 134, p. 221-242, 1857.

GORDON, K. B. ; RUGO, H. S. ; DUNCAN, J. L. et al. Ocular manifestations of leukemia: leukemic infiltration versus infectious process. **Ophthalmology,** [s.l.], p. 2293-2300, Dec. 2001.

HONG, S. S.; PARK, H. R. ; KIM, K. S. et al. Late Effects, Social Adjustment, and Quality of Life in Adolescent Survivors of Childhood Leukemia. **Journal Of Korean Academy Of Nursing,** [s.l.], v. 44, n. 1, p.55-63, 2014. Korean Society of Nursing Science (KAMJE). http://dx.doi.org/10.4040/jkan.2014.44.1.55.

HOVLAN, K. R.; ELLIS, P. P. Ocular changes in renal transplant patients. **Am J Ophtalmol**, v. 63, n. 2, p. 283-289.

HOWARD, S. C.; METZGER, M. L.; WILIMAS, J. A. et al. Childhood Cancer Epidemiology in Low-Income Countries. **Cancer,** v. 112, n. 3, p. 461-472, 2008.

HYMAN, C. B.; BOGLE, J. M.; BRUBAKER, C.A. et al. Central nervous system involvement by leukaemia in children. **Blood,** v. 25, p. 1–12, 1965.

KASMANN, B.; RUPRECHT, K.W. Ophthalmologic findings in graft versus host disease (GvHD). **Klin Monatsbl Augenheilkd,** v. 202, p. 491–499, 1993.

KERSEY, J. P.; BROADWAY, D. C. Corticosteroid-induced glaucoma: a review of the literature. **Eye,** [s.l.], v. 20, n. 4, p.407-416, 6 May 2005. Springer Nature. http://dx.doi.org/10.1038/sj.eye.6701895.

KHADKA, D.; SHARMA, A. K.; SHRESTHA, J. K. et al. Ocular manifestations of childhooh acute leukemia in a tertilary level eye centre of Kathmandu, Nepal. **Nepal J Ophtalmol**., v. 6, n. 2, p. 197-204, Jul./Dec. 2014.

KINCAID, M. C.; GREEN, W. R. Ocular and orbital involvement in leukemia. **Survey Of Ophthalmology,** [s.l.], v. 27, n. 4, p.211-232, Jan. 1983. Elsevier BV. http://dx.doi.org/10.1016/0039-6257(83)90123-6.

KUWABARA, T.; AIELLO, L. Leukaemic military nodule in retina. **Arch Ophthalmol,** v. 72, p. 494–497, 1964.

JABS, D. A.; HIRST, L. W.; GREEN, W. R. et al. The eye in bone marrow transplantation. II. **Histopathology. Arch Ophthalmol,** v. 101, p. 585–590, 1983.

JAKOBIEC, F. A.; JONES, I. S. Lymphomatous plasmacytic, histiocytic, haematopoietic tumours. In: JONES, I. S.; JAKOBIEC, F. A. (eds). **Diseases of the Orbit**. Hagerstown Md, Harper and Row, 1979. p. 309 (see pp 345-348).

LEE, P.-F. The Influence of Systemic Steroid Therapy on the Intraocular Pressure*. **American Journal Of Ophthalmology,** [s.l.], v. 46, n. 3, p.328-331, set. 1958. Elsevier BV. http://dx.doi.org/10.1016/0002-9394(58)90256-3

LIN, H. F.; DAI, M. S.; KAO, W. Y. et al. Unilateral Optic Nerve Leukaemic Infiltration with Sudden Vision Loss Heralding a Systemic Relapse of Acute Lymphoblastic Leukemia. **J Med Sci**, v. 25, n. 2, p. 97-100, 2005.

LINET, M. S.; BROWN, L. M.; MBULAITEYE, S. M. et al. International long-term trends and recent patterns in the incidence of leukemias and lymphomas among children and adolescents ages 0–19 years. **Int J Cancer,** v. 138, p. 1872–1874, 2015.

LINS, M. M. ; SANTOS, M. O. ; DE ALBUQUERQUE, M. F. P. M. et al. Incidence and survival of childhood leukemia in Recife, Brazil: A population-based analysis. **Pediatric Blood & Cancer,** [s.l.], v. 64, n. 8, p.1-6, 21 Dec. 2016. Wiley-Blackwell. http://dx.doi.org/10.1002/pbc.26391.

MARCOUX, S.; DROUIN, S. ; LAVERDIÈRE, C. et al. The PETALE study: Late adverse effects and biomarkers in childhood acute lymphoblastic leukemia survivors. **Pediatric Blood & Cancer,** [s.l.], v. 64, n. 6, p.1-8, 4 Dec. 2016. Wiley-Blackwell. http://dx.doi.org/10.1002/pbc.26361.

MARGOLIN, J.; RABIN, K. R.; STEUBER, C. P. et al. Acute lymphoblastic leukemia. In: PIZZO, P.A.; POPLACK, D. G. eds. **Principles and Practice of Pediatric Oncology.** 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2010. p. 518-565.

MCLEAN, J. M. Use of ACTH and cortisone. **Trans Am Ophthamol Soc**, v. 48, p. 293-296, 1950.

MENDONÇA, C. Q. ; DE SOUZA, C. P.; MARTINS-FILHO, P. R. et al. Steroid-induced ocular hypertensive response in children and adolescents with acute lymphoblastic leukemia and non-hodgkin lymphoma. **Pediatric Blood & Cancer,** [s.l.], v. 61, n. 11, p.2083-2085, 17 Aug. 2014. Wiley-Blackwell. http://dx.doi.org/10.1002/pbc.25070

MEREDITH, T. A.; AABERG, T. M.; REESER, F. H. Rhegmatogenous retinal detachment complicating CMV retinitis. **Am J Ophthalmol**, v. 87, p. 793–796, 1979.

MERTENS, A. C.; BRAND, S.; NESS, K. et al. Health and well-being in adolescent survivors of early childhood cancer: a report from the Childhood Cancer Survivor Study. **Psycho-oncology,** [s.l.], v. 23, n. 3, p.266-275, 4 out. 2013. Wiley-Blackwell. http://dx.doi.org/10.1002/pon.3414.

MORENO, F.; LORIA, D.; ABRIATA, G. et al. Childhood cancer: incidence and early deaths in Argentina, 2000–2008. **Eur J Cancer**, v. 49, p. 465–473, 2013.

NG, P. C.; LEE, C. H. ; TAM, B. S. et al. Transient Increase in Intraocular Pressure during a Dose-Tapering Regime of Systemic Dexamethasone in Preterm Infants. **Ophthalmology,** [s.l.], v. 115, n. 5, p.7-14, maio 2008. Elsevier BV. http://dx.doi.org/10.1016/j.ophtha.2008.01.010

NGUYEN, H. S.; HAIDER, K. M.; ACKERMAN, L. L.Unusual causes of papilledema: Two illustrative cases. **Surg Neurol Int**, v. 4, p. 60, 2013.

PERRY, H. D.; MALLEN, F. J. Iris involvement in granulocytic sarcoma. **Am J Ophthalmol** v. 87, p. 530–532, 1979.

PFEFFER, B. A.; DeWITT, C. A. ; SALVADOR-SILVA, M. et al. Reduced Myocilin Expression in Cultured Monkey Trabecular Meshwork Cells Induced by a Selective Glucocorticoid Receptor Agonist: Comparison with Steroids. **Investigative Opthalmology & Visual Science,** [s.l.], v. 51, n. 1, p.437-446, 1 jan. 2010. Association for Research in Vision and Ophthalmology (ARVO). http://dx.doi.org/10.1167/iovs.09-4202.

PILBEAM, K.; SALVI, S.; HAVANI, A. Corticosteroid-induce glaucoma as a complication of induction therapy in a child with acute lymphoblastic leukemia (ALL). **Pediatr Blood Cancer**, v. 58, p. 1014-1097, 2012.

POMORSKA, M.; KRZYŻANOWSKA-BERKOWSKA, P.; MISIUK-HOJŁO, M. et al. Application of optical coherence tomography in glaucoma suspect eyes. **Clinical And Experimental Optometry,** [s.l.], v. 95, n. 1, p.78-88, 10 Oct. 2011. Wiley-Blackwell. http://dx.doi.org/10.1111/j.1444-0938.2011.00654.x.

QASHTON, A. P. Advances in Ocular Hypertension Research and Treatment: 2011 Edition, **Scholarly Brief**, Atlanta, Georgia: Edition, ScholarlyBrief, 2011. p. 68-69.

RAVINDRANATHAN, M. P.; PAUL, V. J.; KURIAKOSE, E. T. Cataract after busulphan treatment. **Br Med J,** v. 1, n. 218–219, 1972.

RAZEGHINEJAD, M. R.; KATZ, L. J. Steroid-Induced Iatrogenic Glaucoma. **Ophthalmic Research,** [s.l.], v. 47, n. 2, p. 66-80, 2012. http://dx.doi.org/10.1159/000328630

REESE, A. B.; GUY, L. Exophthalmos in leukaemia. **Am J Ophthalmol,** v.16, p. 718–720, 1933.

REDDY, S. C.; MENON, B. S. A prospective study of ocular manifestations in childhood acute leukaemia. **Acta Ophthalmologica Scandinavica,** [s.l.], v. 76, n. 6, p.700-703, Dec. 1998. Wiley-Blackwell. http://dx.doi.org/10.1034/j.1600-0420.1998.760614.x

RIDGWAY, E. W.; JAFFE, N.; WALTON, D. S. Leukemic ophthalmopathy in children. **Cancer,** v. 38, p. 1744–1746, 1976.

ROWAN, P. J.; SLOAN, J. B. Iris and Anterior chamber involvement in leukaemia. **Ann Ophthalmol,** v. 8, p. 1081–1085, 1976.

RUSSO, A.; RIVA, I.; PIZZOLANTE, T. et al. Latanoprost ophthalmic solution in the treatment of open angle glaucoma or raised intraocularpressure: a review. **Clin Ophthalmol**., v. 2, n. 4, p. 897-905, Dec. 2008.

SCHWARTZ, B.; ROM, M. E. ; BEALKA, N. et al. Dose Response of Dexamethasone for the Enhanced Ocular Hypotensive Response to Epinephrine in Rabbits With Prior Dexamethasone Treatment. **Journal Of Ocular Pharmacology And Therapeutics,** [s.l.], v. 18, n. 2, p.133-139, Apr. 2002. Mary Ann Liebert Inc. http://dx.doi.org/10.1089/108076802317373897

SHARMA, T.; GREWAL, J. ; GUPTA, S. et al. Ophthalmic manifestations of acute leukaemias: the ophthalmologist's role. **Eye,** [s.l.], v. 18, n. 7, p. 663-672, 27 Feb. 2004. Springer Nature. http://dx.doi.org/10.1038/sj.eye.6701308.

SHAW, R. K.; MOORE, E. W.; FREIREICH, E. J. et al. Meningeal leukaemia. **Neurology**, v. 10, p. 823–833, 1960.

SHIBATA, K.; SHIMAMOTO, Y.; NISHIMURA, T. et al. Ocular manifestation in adult T cell leukaemia/lymphoma. **Ann Hematol**, v. 74, p. 163–168, 1997.

SHURIN, S. B.; REKATE, H. L.; ANNABLE, W. Optic atrophy induced by vincristine. **Pediatrics,** v. 70, p. 288–291, 1982.

SHUYUAN, L. Y. U.; MING, Z.; YUNXIA, G. A. O. Acute bilateral retina hemorrhages beneath internal limiting membrane: An unusual ophthalmological case report of acute leukemia during complete clinical remission. **Medicine**, v. 97, n. 7, p.e0000, Feb. 2018.

SOYLU, M.; OZDEMIR, G.; ANLI, A. Pediatric uveitis in southern Turkey. **Ocul Immunol Inflamm,** v. 5, p. 197–202, 1997.

SPAETH, G. L.; BARROS, D. S. M.; FUDEMBERG, S. J. Visual Loss Caused by Corticosteroid-Induced Glaucoma: How to Avoid It. **Retina,** [s.l.], v. 29, n. 8, p.1057-1061, Sept. 2009. Ovid Technologies (Wolters Kluwer Health). http://dx.doi.org/10.1097/iae.0b013e3181b32cfd.

STAMER, W. D. ; HOFFMAN, E. A. ; KURALI, E. et al. Unique Response Profile of Trabecular Meshwork Cells to the Novel Selective Glucocorticoid Receptor Agonist, GW870086X. **Investigative Opthalmology & Visual Science,** [s.l.], v. 54, n. 3, p. 2100-2107, 27 Mar. 2013. Association for Research in Vision and Ophthalmology (ARVO). http://dx.doi.org/10.1167/iovs.12-11298

TALCOTT, K. E.; GARG, R. J.; GARG, S. J. Ophthalmic manifestations of leukemia. **Current Opinion In Ophthalmology,** [s.l.], v. 27, n. 6, p.545-551, Nov. 2016. Ovid Technologies (Wolters Kluwer Health). http://dx.doi.org/10.1097/icu.0000000000000309

TERWILLIGER, T.; ABDUL-HAY, M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. **Blood Cancer Journal,** [s.l.], v. 7, n. 6, p.577-577, 30 Jun. 2017. Springer Nature. http://dx.doi.org/10.1038/bcj.2017.53.

THAM, C. C. Y. ; NG, J. S. K. ; LI, R. T. H. et al. Intraocular pressure profile of a child on a systemic corticosteroid. **American Journal Of Ophthalmology,** [s.l.], v. 137, n. 1, p.198-201, Jan. 2004. Elsevier BV. http://dx.doi.org/10.1016/s0002-9394(03)00838-9.

TRIPATHI, R. C. ; KIRSCHNER, B. S. ; KIPP, M. et al. Corticosteroid treatment for inflammatory bowel disease in pediatric patients increases intraocular pressure. **Gastroenterology**, v. 102, n. 6, p. 1957–1961, 1992.

URBAN, R. C.; DREYER, E. B. Corticosteroid-induced glaucoma. **International Ophthalmology Clinics**, v. 33, n. 2, p. 135–139, 1993.

WALTON, R. C.; REED, K. L. Herpes zoster ophthalmicus following bone marrow transplantation in children. **Bone Marrow Transplant,** v. 23, p. 1317–1320, 1999.

WARD, E.; DESANTINS, C. ; ROBBINS, A. et al. Childhood and adolescent cancer statistics, 2014. **Ca: A Cancer Journal for Clinicians**, [s.l.], v. 64, n. 2, p.83-103, 31 Jan. 2014. American Cancer Society. http://dx.doi.org/10.3322/caac.21219.

WATANABE, A. Recent advance in treatmentof childhood acute lymphoblastic leukemia. **Gan to Kagaku Ryoho**, v. 34, p.150-155, 2007.

WHELAN, K. F.; STRATTON, K.; KAWASHIMA, T. et al. Ocular late effects in childhood and adolescent cancer survivors: A report from the childhood cancer survivor study**.** **Pediatric Blood & Cancer**, [s.l.], v. 54, n. 1, p. 103-109, Jan. 2010. Wiley-Blackwell. http://dx.doi.org/10.1002/pbc.22277.

YALCINBAYIR, O.; BAYTAN, B. ; GELISKEN, O. et al. Spectral domain optical coherence tomography findings of patients under treatment for pediatric acute lymphoblastic leukemia. **Journal Of American Association For Pediatric Ophthalmology And Strabismus**, [s.l.], v. 21, n. 2, p.131-135, Apr. 2017. Elsevier BV. http://dx.doi.org/10.1016/j.jaapos.2016.12.002.

YAMASHITA, T.; KODAMA, Y.; TANAKA, M. et al. Steroid-induced Glaucoma in Children With Acute Lymphoblastic Leukemia. **Journal Of Glaucoma,** [s.l.], v. 19, n. 3, p.188-190, Mar. 2010. Ovid Technologies (Wolters Kluwer Health). http://dx.doi.org/10.1097/ijg.0b013e3181af321d

YASMEEN, N.; ASHRAF, S. Childhood acute lymphoblastic leukaemia; epidemiology and clinicopathological features. **JPMA: The Journal of the Pakistan Medical Association**, v. 59, n. 3, p. 150–153, 2009.

YEOH, A. J. ; TAN, D. ; LI, C. K. et al. Management of adult and paediatric acute lymphoblastic leukaemia in Asia: resource-stratified guidelines from the Asian Oncology Summit 2013. **The Lancet Oncology,** [s.l.], v. 14, n. 12, p. 508-523, Nov. 2013. Elsevier BV. http://dx.doi.org/10.1016/s1470-2045(13)70452-2.

YOUNG, J. L.; RIES, L. G.; SILVERBERG, E. et al. Cancer incidence, survival, and mortality for children younger than age 15 years. **Cancer**, v. 58, n. 2, p. 598-602, 1986.

ZHANG, X.; CLARK, A. F.; YORIO, T. Regulation of Glucocorticoid Responsiveness in Glaucomatous Trabecular Meshwork Cells by Glucocorticoid Receptor-β. **Investigative Opthalmology & Visual Science,** [s.l.], v. 46, n. 12, p.62-66, 1 Dec. 2005. Association for Research in Vision and Ophthalmology (ARVO). http://dx.doi.org/10.1167/iovs.05-0571.

PRODUÇÃO CIENTÍFICA

a) **"Steroid-Induced Ocular Hypertensive Response in Children and Adolescents with Acute Lymphoblastic Leukemia and Non-Hodgkin Lymphoma".**
Artigo publicado no "Pediatric Blood and Cancer em 25/03/2014, PBC 25070

b) **"Ocular Manifestations in Acute Lymphoblastic Leukemia: A Five-Year Cohort Study of Pediatric Patients".**
Artigo publicado "Leukemia Research, em 29/11/2018, leukres 10.1016.

c) **"Steroid-Induced Ocular Hypertensive Response in Children and Adolescents with Acute Lymphoblastic Leukemia and Non-Hodgkin Lymphoma: a Systematic Review".**
Artigo submetido no "Journal of Pediatric Hematology and Oncology JPHO-18-150. Foram submetidas as correções solicitadas pelos revisores; manuscrito com o Editor, aguardando parecer final.

d) **"Comportamento Da Pressão Ocular Em Pacientes Pediátricos Tratados Para Leucemia Linfoblástica Aguda E Linfoma Não Hodgkin".**
Apresentado no Congresso Brasileiro de Hematologia, Hemoterapia e Terapia Celular -Hemo 2014.

e) **"Ocular Hypertension In Pediatric Patients Treated for Acute Lymphoblastic Leukemia and Non-Hodkin Lymphoma"**

Apresentado no 48º Congress of the International Society of Pediatric Oncology, Dublin-Irlanda, SIOP 2016.

f) **“Manifestações Oculares Em Leucemia Linfoblástica Aguda: Estudo De Coorte Em Pacientes Pediátricos Durante Cinco Anos”.**
Apresentado no Congresso Brasileiro de Hematologia, Hemoterapia e Terapia Celular -Hemo 2018.

g) **“Dissertação de Mestrado”**

- Cristiano de Queiroz Mendonça - UFS.
- Marcelle Vieira Freire - UFS.

h)**"Retinopatia Leucêmica: Relato de Caso".**

Apresentado no IX Congresso Nacional da Sociedade Brasileira de Oftalmologia – 2017

i) **“Trabalhos de Conclusão de Curso (TCC)”:**

- Celso de Souza Dias Júnior - UFS.
- Cristiano Prado de Souza Júnior - UFS.
- Mayo Kayann Guerra Silva Tavares - UFS.
- Marcelle Vieira Freire - UFS.
- Marcus Vinícius Prado Guerreiro Filho - UNIT.
- Paulo Cesar Machado Filho - UNIT.
- Rafael Sucupira Menezes - UNIT.
- Wallace Marcelo Almeida Silva - UFS.

APÊNDICE A - Termo de Consentimento Livre e Esclarecido

Prezado(a) Sr(a)_____

Meu nome é Cristiano de Queiroz Mendonça, sou Médico Oftalmologista, aluno do doutorado em Ciências da Saúde da Universidade Federal de Sergipe, tendo como orientadora no projeto de pesquisa a Professora Doutora Rosana Cipolotti.

Em virtude de poucos estudos sobre as alterações oftalmológicas e a alta prevalência dessa patologia no Brasil, fica evidente a necessidade de novas pesquisas para melhoria da qualidade de vida destes pacientes.

Assim, através deste documento, estou solicitando ao Sr (a) a liberação dos resultados dos exames que estão nos prontuários regularmente cadastrados no Ambulatório de Oncologia Pediátrica, bem como a solicitação para a realização de exame de medida da pressão intra ocular por método não invasivo de Tonometria de Aplanação, com instilação de gotas de colírio com efeito anestésico e corante de Fluoresceina. A curvatura e elevação corneana por imagem obtida pelo aparelho Pentacam HR e a análise das fibras nervosas retinianas por aparelho de Tomógrafo de Coerência Óptica, sem contato direto ocular e posterior análise em programas específicos dos aparelhos. Garantindo-se que não haverá qualquer identificação do nome do (a) paciente, afirmo desde já, que se trata de um trabalho de pesquisa e como tal, a

sua participação é voluntária, estando garantido o seu direito ao tratamento em qualquer situação. Além disso, mesmo concordando, o (a) senhor (a) pode desistir a qualquer momento, sem prejuízo para o tratamento.

Em caso de dúvida, entre em contato imediatamente conosco, nos ambulatórios onde costuma ser atendido, ou por um dos telefones anotados abaixo. Muito obrigado.

Responsável:_____

_____

Dr Cristiano de Queiroz Mendonça Tel: 981019901

Doutorando

_____

Drª Rosana Cipolotti Tel: 99811238

Orientadora Data:_____

ANEXO A – PARECER CONSUBSTANCIADO CEP/UFS

Hospital Universitário / Universidade Federal de Sergipe

Parecer consubstanciado do CEP

Dados do projeto de pesquisa título da pesquisa: comportamento da pressão ocular em pacientes pediátricos

Tratados para leucemia linfoblástica aguda e linfoma não hodgkin pesquisador: Cristiano MENdonça

Área temática: versão: 1caae: 13317113.0.0000.5546instituição proponente: fundacao universidade federal de sergipe patrocinador principal: financiamento próprio

Dados do parecer número do parecer: 214.759

Data da relatoria: 01/03/2013

Apresentação do projeto:

Trata-se de estudo de pesquisa do tipo descritivo, observacional, longitudinal a ser realizado em crianças e adolescentes, ambos os sexos, na faixa etária entre 05 e 18 anos de idade, com diagnóstico de lla e lnh, matriculados no centro de oncologia de sergipe dr. Oswaldo leite como tratamento inicial. A incluysão se dará por confirmação cito-histopatológica do diagnóstico e consentimento do responsável. A amostra será de 50 pacientes por um periodo de 12 meses de coleta. Apresenta critérios de inclusão e critérios de exclusão.

Os dados obtidos serão armazenados em banco de dados padronizado. Os descritivos serão expressos em medidas de tendência central (média e desvio-padrão ou mediana). As comparações entre os grupos serão feitas pelos testes de proporções (qui-quadrado ou exato de fisher) e de testes de médias (anova, teste t para amostras independentes ou Pareadas) e análise multivariada para p>0,05.

Objetivo da pesquisa:

Objetivo primário: avaliar o comportamento da pressão intraocular em pacientes pediátricos portadores de neoplasias linfoproliferativas agudas tratados com glicocorticóides, nas diferentes fases do protocolo terapêutico.objetivo secundário:associar os achados com variáveis metabólicas relacionadas ao uso de glicocorticoides. Identificar eventuais interferências sobre a função visual.

Endereço: rua cláudio batista s/no bairro: sanatório

Cep: 49.060-110e-mail: cephu@ufs.br

Uf: se município: telefone: (79) 2105-1805

Aracaju

Avaliação dos riscos e benefícios:

Os riscos foram considerados desprezíveis pelos pesquisadores, limitado ao desconforto da aplicação de colírio anetésico associado ao corante de fluoresceína. Considerado risco mínimo de infecção, semelhante a da instilação ocular de qualquer medicamento benefícios: diagnosticar e evitar quaisquer alterações visuais consequente a hiperetensão ocular

secundária ao tratamento para leucemia linfoblástica aguda e linfoma não hodgkin

Comentários e considerações sobre a pesquisa:

O projeto de pesquisa apresenta delineamwento adequado com base na literatura científica. Método, contempla o desenho de estudo em todos os seus aspectos, local de estudo, seleção da amostra, critérios de inclusão e exclusão, procedimentos da coleta de dados e seus respectivos instrumentos e, a análise estatística.

Cronograma adequado ao estudo. Orçamento, planilha identifica os custos da pesquisa e declara ser de responsabilidade dos pesquisadores apesar de seu custo bastante expressivo (r$ 37.705,00), assim descrito: o grupo de pesquisa já possui os equipamentos pentacam e tomógrafo de coerência óptica, sendo os exames realizados sem custo adicional. Os exames de glicemia fazem parte do protocolo de tratamento e são custeados pelo sus. O materia de consumo será custeado pelos pesquisadores.

Considerações sobre os termos de apresentação obrigatória:

Folha de rosto: preenchimento adequado pelo pesquisador e pela instituição proponente nucleo de pós- graduação em medicina. autorização do centro de oncologia de sergipe dr. Osvaldo leite do hospital de urgências de sergipe, datada e assinada pelo responsável

Tcle atende o que determina a res 196/96/cns: linguagem clara com as informações pertinentes, objetivos, riscos e benefícios, direito de desistir da participação sem prejuízo ao tratamento, o sigilo, o caráter de confiabilidade estão assegurados, contatos dos pesquisadores.

Recomendações:

Sugiro correção no TCLE identificar local para assinatura do responsável ou representante legal

Conclusões ou pendências e lista de inadequações:

Tcle identificar local para assinatura do responsável ou representante legal

Situação do parecer:

Aprovado

Necessita apreciação da conep:

Não

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